

# THE AMERICAN JOURNAL OF PSYCHIATRY

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Official Journal of the American Psychiatric Association



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benzodiazepine  
withdrawal  
syndrome when  
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**References:** 1. Rickels K, et al. Buspirone and diazepam in anxiety: A controlled study. *J Clin Psychiatry* 1982; 43(12, Sec 2): 81-86. 2. Newton RE, et al. A review of the side effect profile of buspirone. *Am J Med* 1986; 80(suppl 3B): 17-21. 3. Lucki I, et al. Differential effects of the anxiolytic drugs, diazepam and buspirone, on memory function. *Br J Clin Pharmacol* 1987; 23: 207-211. 4. Lader M. Assessing the potential for buspirone dependence or abuse and effects of its withdrawal. *Am J Med* 1987; 82(suppl 5A): 20-26.

**Contraindications:** Hypersensitivity to buspirone hydrochloride.

**Warnings:** The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended. BuSpar should not be employed in lieu of appropriate antipsychotic treatment.

**Precautions: General—Interference with cognitive and motor performance:** Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable; therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely. Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.

**Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients:** Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life. The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

**Possible concerns related to buspirone's binding to dopamine receptors:** Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (eg, dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported; the

syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (ie, represent akathisia).

**Information for Patients—**Patients should be instructed to inform their physician about any medications, prescription or nonprescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone; to inform their physician if they are breast feeding, and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

**Drug Interactions—**Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**). Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. Concomitant administration of BuSpar and haloperidol resulted in increased serum haloperidol concentrations in normal volunteers. The clinical significance is not clear. Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin. However, there was one report of prolonged prothrombin time when buspirone was given to a patient also treated with warfarin, phenytoin, phenobarbital, digoxin, and Synthroid.

**Carcinogenesis, Mutagenesis, Impairment of Fertility—**No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chromosomal aberrations or abnormalities did not occur.

**Pregnancy: Teratogenic Effects—**Pregnancy Category B: Should be used during pregnancy only if clearly needed.

**Nursing Mothers—**Administration to nursing women should be avoided if clinically possible.

**Pediatric Use—**The safety and effectiveness have not been determined in individuals below 18 years of age.

**Use in the Elderly—**No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg.

**Use in Patients with Impaired Hepatic or Renal Function—**Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.

**Adverse Reactions (See also Precautions): Commonly Observed—**The more commonly observed untoward events, not seen at an equivalent incidence in placebo-treated patients, include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.

**Associated with Discontinuation of Treatment—**The more common events causing discontinuation in-



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### Well tolerated

The more commonly observed untoward events associated with the use of BuSpar not seen at an equivalent incidence among placebo-treated patients include dizziness (12%), nausea (8%), headache (6%), nervousness (5%), lightheadedness (3%), and excitement (2%).

\*Because the effects of BuSpar in any individual patient may not be predictable, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that BuSpar treatment does not affect them adversely.

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cluded: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling; gastrointestinal disturbances (1.2%), primarily nausea; miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

**Incidence in Controlled Clinical Trials**—Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials: *Cardiovascular*: tachycardia/palpitations 1%. *CNS*: Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. *EENT*: Blurred vision 2%. *Gastrointestinal*: Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. *Musculoskeletal*: Musculoskeletal aches/pains 1%. *Neurological*: Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. *Skin*: Skin rash 1%. *Miscellaneous*: Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

**Other Events Observed During the Entire Premarketing Evaluation**—The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients; and rare are those occurring in less than 1/1000 patients. *Cardiovascular*—frequent: non-specific chest pain; infrequent: syncope, hypotension, hypertension; rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia. *Central Nervous System*—frequent: dream disturbances; infrequent: depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation, seizures; rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis. *EENT*—frequent: tinnitus, sore throat, nasal congestion; infrequent: redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes. *Endocrine*—rare: galactorrhea, thyroid abnormality. *Gastrointestinal*—infrequent: flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding; rare: burning of the tongue. *Genitourinary*—infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia. *Musculoskeletal*—infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. *Neurological*—infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. *Respiratory*—infrequent: hyperventilation, shortness of

breath, chest congestion; rare: epistaxis. *Sexual Function*—infrequent: decreased or increased libido; rare: delayed ejaculation, impotence. *Skin*—infrequent: edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails. *Clinical Laboratory*—infrequent: increases in hepatic aminotransferases (SGOT, SGPT); rare: eosinophilia, leukopenia, thrombocytopenia. *Miscellaneous*—infrequent: weight gain, fever, roaring sensation in the head, weight loss, malaise; rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs.

**Postintroduction Clinical Experience**—Rare occurrences of allergic reactions, cogwheel rigidity, dystonic reactions, ecchymosis, emotional lability, tunnel vision, and urinary retention have been reported. Because of the uncontrolled nature of these spontaneous reports, a causal relationship to BuSpar has not been determined.

**Drug Abuse and Dependence: Controlled Substance Class**—Not a controlled substance.

**Physical and Psychological Dependence**—Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

**Overdose: Signs and Symptoms**—At doses approaching 375 mg/day the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdose.

**Recommended Overdose Treatment**—General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative.

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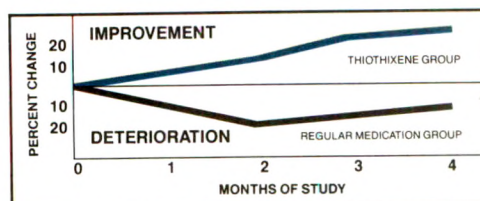


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**References:** 1. Bressler B, Friedel RO: A comparison between chlorpromazine and thiothixene in a Veterans Administration hospital population. *Psychosomatics* 1971;12:275-277. 2. DiMascio A, Demirgian E: Study of the activating properties of thiothixene. *Psychosomatics* 1972;13:105-108. 3. DiMascio A, Demirgian E: Job training in the rehabilitation of the chronic schizophrenic. Presented as a Scientific Exhibit at The American Psychiatric Association, Washington, DC, May 3-6, 1971. 4. Goldstein B, Weiner D, Banas F: Clinical evaluation of thiothixene in chronic ambulatory schizophrenic patients, in Lehmann HE, Ban TA (eds): *The Thioxanthenes: Modern Problems of Pharmacopsychiatry*. Basel, Switzerland, S. Karger, 1969, vol 2, pp 45-52. 5. Dillenkoff RL, Gallant DM, George RB, et al: Electrocardiographic evaluation of schizophrenic patients: A double-blind comparison. Presented as a Scientific Exhibit at The 125th Annual Meeting of the American Psychiatric Association, Dallas, May 1-4, 1972. 6. Data available on request from Roerig.

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**Warnings:** **Tardive Dyskinesia**—Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that: 1) is known to respond to neuroleptic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to Information for Patients in the Precautions section, and to the Adverse Reactions section.)

**Neuroleptic Malignant Syndrome (NMS)**—A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reinstitution of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

**Use in Pregnancy**—Safe use of Navane during pregnancy has not been established. Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus. Animal reproduction studies and clinical experience to date have not demonstrated any teratogenic effects.

In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents. After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen. (See Precautions.)

**Use in Children**—The use of Navane in children under 12 years of age is not recommended because safety and efficacy in the pediatric age group have not been established.

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol.

**Precautions:** An antiemetic effect was observed in animal studies with Navane, since this effect may also occur in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumor.

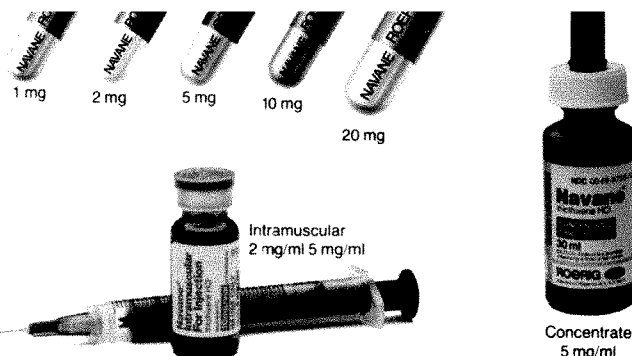
In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold. Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered concurrently.

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with other CNS depressants other than anticonvulsant drugs.

Though Navane has rather weak anticholinergic properties, Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving other anticholinergic drugs.

Use with caution in patients with cardiovascular disease.

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine lenticular pigmentation) has been noted in a small number of patients treated with Navane for prolonged



periods). Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenic purpura), and liver damage (jaundice, biliary stasis) have been reported with related drugs.

Undue exposure to sunlight should be avoided. Photosensitive reactions have been reported in patients on Navane (thiothixene).

**Intramuscular Administration**—As with all intramuscular preparations, Navane intramuscular should be injected well within the body of a relatively large muscle. The preferred sites are the upper outer quadrant of the buttock (i.e. gluteus maximus) and the mid-lateral thigh.

The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-thirds of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecostasia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

**Information for Patients**—Given the likelihood that some patients exposed chronically to neuroleptics will develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, if possible, full information about this risk. The decision to inform patients and/or their guardians must obviously take into account the clinical circumstances and the competency of the patient to understand the information provided.

**Adverse Reactions:** Note: Not all of the following adverse reactions have been reported with Navane (thiothixene). However, since Navane has certain chemical and pharmacologic similarities to the phenothiazines, all of the known side effects and toxicity associated with phenothiazine therapy should be borne in mind when Navane is used.

**Cardiovascular effects:** Tachycardia, hypotension, lightheadedness, and syncope. In the event hypotension occurs, epinephrine should not be used as a pressor agent since a paradoxical further lowering of blood pressure may result. Nonspecific EKG changes have been observed in some patients receiving Navane (thiothixene). These changes are usually reversible and frequently disappear on continued Navane therapy. The incidence of these changes is lower than that observed with some phenothiazines. The clinical significance of these changes is not known.

**CNS effects:** Drowsiness, usually mild, may occur although it usually subsides with continuation of Navane therapy. The incidence of sedation appears similar to that of the piperazine group of phenothiazines, but less than that of certain aliphatic phenothiazines. Restlessness, agitation and insomnia have been noted with Navane. Seizures and paradoxical exacerbation of psychotic symptoms have occurred with Navane infrequently.

Hyperreflexia has been reported in infants delivered from mothers having received structurally related drugs.

In addition, phenothiazine derivatives have been associated with cerebral edema and cerebrospinal fluid abnormalities.

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia, and dystonia have been reported. Management of these extrapyramidal symptoms depends upon the type and severity. Rapid relief of acute symptoms may require the use of an injectable antiparkinson agent. More slowly emerging symptoms may be managed by reducing the dosage of Navane and/or administering an oral antiparkinson agent.

Persistent tardive dyskinesia: As with all antipsychotic agents tardive dyskinesia may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities.

Since early detection of tardive dyskinesia is important, patients should be monitored on an ongoing basis. It has been reported that fine vermicular movement of the tongue may be an early sign of the syndrome. If this or any other presentation of the syndrome is observed, the clinician should consider possible discontinuation of neuroleptic medication. (See Warnings section.)

**Hepatic Effects:** Elevations of serum transaminase and alkaline phosphatase, usually transient, have been infrequently observed in some patients. No clinically confirmed cases of jaundice attributable to Navane have been reported.

**Hematologic Effects:** As is true with certain other psychotropic drugs, leukopenia and leukocytosis, which are usually transient, can occur occasionally with Navane. Other antipsychotic drugs have been associated with agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopenia.

**Allergic Reactions:** Rash, pruritus, urticaria, photosensitivity and rare cases of anaphylaxis have been reported with Navane. Undue exposure to sunlight should be avoided. Although not experienced with Navane, exfoliative dermatitis and contact dermatitis (in nursing personnel) have been reported with certain phenothiazines.

**Endocrine Disorders:** Lactation, moderate breast enlargement and amenorrhea have occurred in a small percentage of females receiving Navane. If persistent, this may necessitate a reduction in dosage or the discontinuation of therapy. Phenothiazines have been associated with false positive pregnancy tests, gynecostasia, hypoglycemia, hyperglycemia, and glycosuria.

**Autonomic Effects:** Dry mouth, blurred vision, nasal congestion, constipation, increased sweating, increased salivation, and impotence have occurred infrequently with Navane therapy. Phenothiazines have been associated with miosis, mydriasis, and adynamic ileus.

**Other Adverse Reactions:** Hyperpyrexia, anorexia, nausea, vomiting, diarrhea, increase in appetite and weight, weakness or fatigue, polydipsia and peripheral edema.

Although not reported with Navane, evidence indicates there is a relationship between phenothiazine therapy and the occurrence of a systemic lupus erythematosus-like syndrome.

**Neuroleptic Malignant Syndrome (NMS)** Please refer to the text regarding NMS in the WARNINGS section.

**NOTE:** Sudden deaths have occasionally been reported in patients who have received certain phenothiazine derivatives. In some cases the cause of death was apparently cardiac arrest or asphyxia due to failure of the cough reflex. In others, the cause could not be determined nor could it be established that death was due to phenothiazine administration.

**Dosage:** Dosage of Navane should be individually adjusted depending on the chronicity and severity of the condition. See full prescribing information.

**Overdosage:** For information on signs and symptoms, and treatment of overdosage, see full prescribing information.

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New York, New York 10017

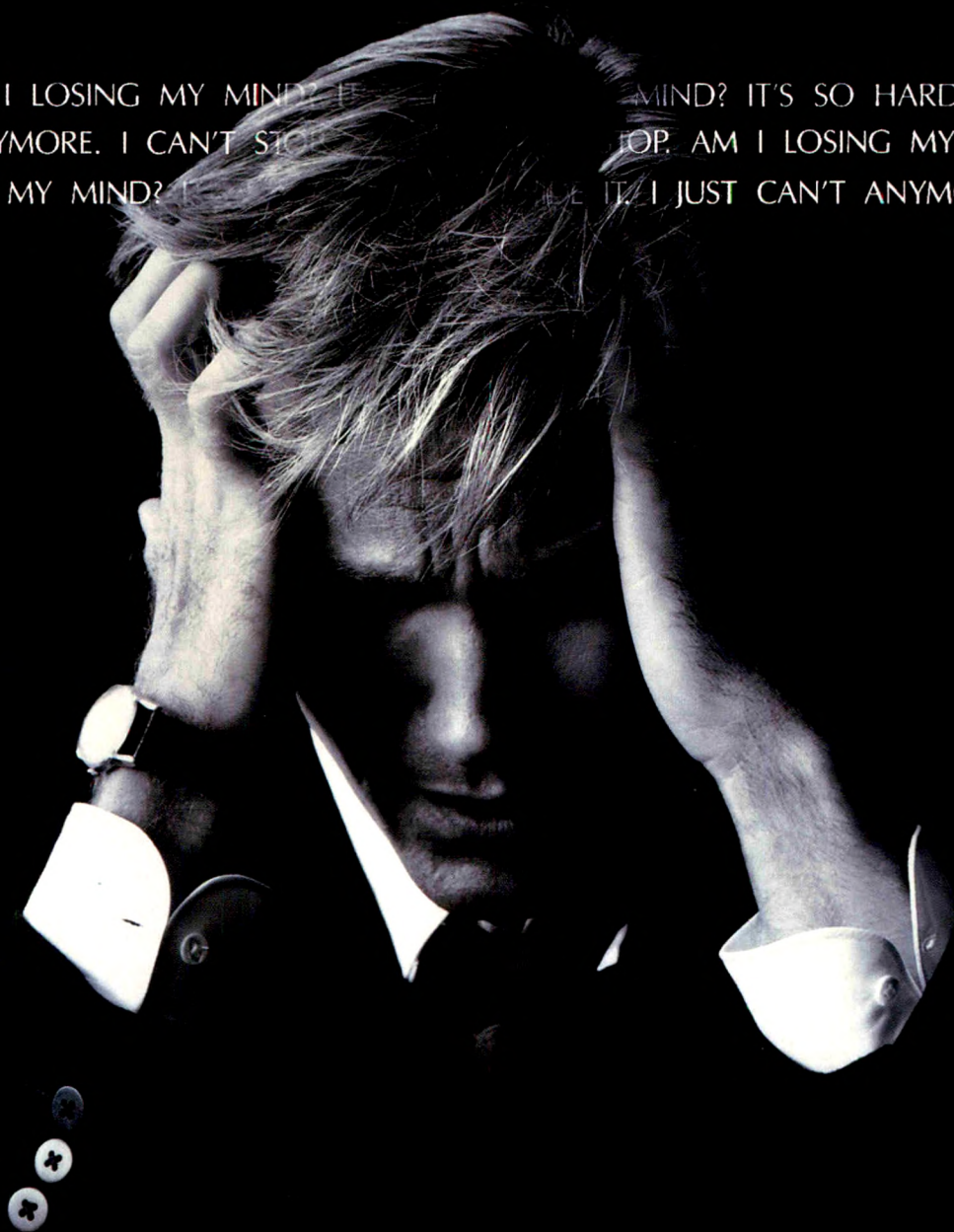


# NEW

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## Powerful medicine to stop intrusive thoughts and acts

OP. AM I LOSING MY MIND? IT'S SO HARD TO HIDE IT. I JUST CAN'T ANYMORE. I CAN'T STOP IT. OP. AM I LOSING MY MIND? IT'S SO HARD TO HIDE IT. I JUST CAN'T ANYMORE. I CAN'T STOP IT.









INTRODUCING

**NEW**

# **Anafranil<sup>®</sup>**

clomipramine HCl

**Powerful tricyclic therapy for  
obsessive-compulsive disorder**

- ▲ *Relieves obsessions and compulsions in OCD patients with or without concomitant depression*

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***Reduces anxiety-producing intrusive thoughts<sup>1</sup>***

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***Reduces ritualized behavior<sup>1</sup>***

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- ▲ *Dual mode of action creates a unique treatment role*

*Anafranil is believed to block the reuptake of serotonin and norepinephrine.<sup>2,3</sup>*

- ▲ *Safety and tolerability demonstrated in over 20 years of worldwide use*

***Symptoms are substantially reduced in approximately 58% of patients.<sup>4</sup>***

*The most common adverse events are dry mouth, somnolence, tremor, dizziness, constipation, and ejaculatory failure. Anafranil may lower the seizure threshold. See warnings and full Prescribing Information on the following pages.*

**References:** **1.** DeVeaugh-Geiss J, Landau P, Katz R. Treatment of obsessive-compulsive disorder with clomipramine. *Psychiatr Ann.* 1989;19:97-101. **2.** Insel TR, Murphy DL, Cohen RM et al. Obsessive-compulsive disorder: A double-blind trial of clomipramine and clorgyline. *Arch Gen Psychiatry.* 1983;40:605-611. **3.** Zohar J, Insel TR, Zohar-Kadouch RC et al. Serotonergic responsivity in obsessive-compulsive disorder. *Arch Gen Psychiatry.* 1988;45:167-171. **4.** Data on file, CIBA-GEIGY Corporation.

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**CIBA-GEIGY**

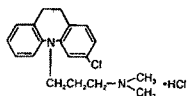


# Anafranil® clomipramine hydrochloride Capsules

## Prescribing Information

### DESCRIPTION

Anafranil, clomipramine hydrochloride, is an antidepressant drug that belongs to the class (dibenzazepine) of pharmacologic agents known as tricyclic antidepressants. Anafranil is available as capsules of 25, 50, and 75 mg for oral administration. Clomipramine hydrochloride is 3-chloro-5-[3-(dimethylamino)propyl]-10,11-dihydro-5H-dibenz[b,f]azepine monohydrochloride, and its structural formula is:



Clomipramine hydrochloride is a white to off-white crystalline powder. It is freely soluble in water, in methanol, and in methylene chloride, and insoluble in ethyl ether and in hexane. Its molecular weight is 351.3.

**Inactive Ingredients.** D&C Red No. 33 (25-mg capsules only), D&C Yellow No. 10, FD&C Blue No. 1 (50-mg capsules only), FD&C Yellow No. 6, gelatin, magnesium stearate, methylparaben, propylparaben, silicon dioxide, sodium lauryl sulfate, starch, and titanium dioxide.

### CLINICAL PHARMACOLOGY

#### Pharmacodynamics

Clomipramine (CMI) is presumed to influence obsessive and compulsive behaviors through its effects on serotonergic neuronal transmission. The actual neurochemical mechanism is unknown, but CMI's relatively selective capacity to inhibit the reuptake of serotonin (5-HT) as compared to norepinephrine (NE) may be important.

#### Pharmacokinetics

**Absorption/Bioavailability.** CMI from Anafranil capsules is as bioavailable as CMI from a solution. The bioavailability of CMI from capsules is not significantly affected by food.

In a dose proportionality study involving multiple CMI doses, steady-state plasma concentrations ( $C_{ss}$ ) and area-under-plasma-concentration-time curves (AUC) of CMI and its major active metabolite, desmethylclomipramine (DMI), were not proportional to dose over the ranges evaluated, i.e., between 25-100 mg/day and between 25-150 mg/day, although  $C_{ss}$  and AUC are approximately linearly related to dose between 100-150 mg/day. The relationship between dose and CMI/DMI concentrations at higher daily doses has not been systematically assessed, but if there is significant dose dependency at doses above 150 mg/day, there is the potential for dramatically higher  $C_{ss}$  and AUC even for patients dosed within the recommended range. This may pose a potential risk to some patients (see WARNINGS and PRECAUTIONS, Drug Interactions).

After a single 50-mg oral dose, maximum plasma concentrations of CMI occur within 2-6 hours (mean, 4.7 hr) and range from 56 ng/ml to 154 ng/ml (mean, 92 ng/ml). After multiple daily doses of 150 mg of Anafranil, steady-state maximum plasma concentrations range from 84 ng/ml to 339 ng/ml (mean, 218 ng/ml) for CMI and from 134 ng/ml to 532 ng/ml (mean, 274 ng/ml) for DMI. No pharmacokinetic information is available for doses ranging from 150 mg/day to 250 mg/day, the maximum recommended daily dose.

**Distribution:** CMI distributes into cerebrospinal fluid (CSF) and brain and into breast milk. DMI also distributes into CSF, with a mean CSF/plasma ratio of 2.6. The protein binding of CMI is approximately 97%, principally to albumin, and is independent of CMI concentration. The interaction between CMI and other highly protein-bound drugs has not been fully evaluated, but may be important (see PRECAUTIONS, Drug Interactions).

**Metabolism:** CMI is extensively biotransformed to DMI and other metabolites and their glucuronide conjugates. DMI is pharmacologically active, but its effects on OCD behaviors are unknown. These metabolites are excreted in urine and feces, following biliary elimination. After a 25-mg radiolabeled dose of CMI in two subjects, 80% and 51%, respectively, of the dose were recovered in the urine and 32% and 24%, respectively, in feces. In the same study, the combined urinary recoveries of CMI and DMI were only about 0.8-1.3% of the dose administered. CMI does not induce drug-metabolizing enzymes, as measured by antipyrine half-life.

**Elimination:** Evidence that the  $C_{ss}$  and AUC for CMI and DMI may increase disproportionately with increasing oral doses suggests that the metabolism of CMI and DMI may be capacity limited. This fact must be considered in assessing the estimates of the pharmacokinetic parameters presented above, as these were obtained in individuals exposed to doses of 150 mg. If the pharmacokinetics of CMI and DMI are nonlinear at doses above 150 mg, their elimination half-lives may be considerably lengthened at doses near the upper end of the recommended dosing range (i.e., 200 mg/day to 250 mg/day). Consequently, CMI and DMI may accumulate, and this accumulation may increase the incidence of any dose- or plasma-concentration-dependent adverse reactions, in particular seizures (see WARNINGS).

After a 150-mg dose, the half-life of CMI ranges from 19 hours to 37 hours (mean, 32 hr) and that of DMI ranges from 54 hours to 77 hours (mean, 69 hr). Steady-state levels after multiple dosing are typically reached within 7-14 days for CMI. Plasma concentrations of the metabolite exceed the parent drug on multiple dosing. After multiple dosing with 150 mg/day, the accumulation factor for CMI is approximately 2.5 and for DMI is 4.6. Importantly, it may take two weeks or longer to achieve this extent of accumulation at constant dosing because of the relatively long elimination half-lives of CMI and DMI (see DOSAGE AND ADMINISTRATION). The effects of hepatic and renal impairment on the disposition of Anafranil have not been determined.

**Pharmacokinetic Interactions:** Coadministration of haloperidol with CMI increases plasma concentrations of CMI. Coadministration of CMI with phenobarbital increases plasma concentrations of phenobarbital (see PRECAUTIONS, Drug Interactions). Younger subjects (18-40 years of age) tolerated CMI better and had significantly lower steady-state plasma concentrations, compared with subjects over 65 years of age. Children under 15 years of age had significantly lower plasma concentration/dose ratios, compared with adults. Plasma concentrations of CMI were significantly higher in smokers than in nonsmokers.

### INDICATIONS AND USAGE

Anafranil is indicated for the treatment of obsessions and compulsions in patients with Obsessive-Compulsive Disorder (OCD). The obsessions or compulsions must cause marked distress, be time-consuming, or significantly interfere with social or occupational functioning, in order to meet the DSM-III-R (circa 1989) diagnosis of OCD.

Obsessions are recurrent, persistent ideas, thoughts, images, or impulses that are ego-dystonic. Compulsions are repetitive, purposeful, and intentional behaviors performed in response to an obsession or in a stereotyped fashion, and are recognized by the person as excessive or unreasonable.

The effectiveness of Anafranil for the treatment of OCD was demonstrated in multicenter, placebo-controlled, parallel-group studies, including two 10-week studies in adults and one 8-week study in children and adolescents 10-17 years of age. Patients in all studies had moderate-to-severe OCD (DSM-III), with mean baseline ratings on the Yale-Brown Obsessive Compulsive Scale (YBOCS) ranging from 26 to 28 and a mean baseline rating of 10 on the NIMH Clinical Global Obsessive Compulsive Scale (NIMH-OC). Patients taking CMI experienced a mean reduction of approximately 10 on the YBOCS, representing an average improvement on this scale of 35% to 42% among adults and 37% among children and adolescents. CMI treated patients experienced a 3.5 unit decrement on the NIMH-OC. Patients on placebo showed no important clinical response on either scale. The maximum dose was 250 mg/day for most adults and 3 mg/kg/day (up to 200 mg) for all children and adolescents.

The effectiveness of Anafranil for long-term use (i.e., for more than 10 weeks) has not been systematically evaluated in placebo-controlled trials. The physician who elects to use Anafranil for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

### CONTRAINDICATIONS

Anafranil is contraindicated in patients with a history of hypersensitivity to Anafranil or other tricyclic antidepressants.

Anafranil should not be given in combination, or within 14 days of treatment, with a monoamine oxidase (MAO) inhibitor. Hyperpyretic crisis, seizures, coma, and death have been reported in patients receiving such combinations.

Anafranil is contraindicated during the acute recovery period after a myocardial infarction.

### WARNINGS

#### Seizures

During premarket evaluation, seizure was identified as the most significant risk of Anafranil use.

The observed cumulative incidence of seizures among patients exposed to Anafranil at doses up to 300 mg/day was 0.64% at 90 days, 1.12% at 180 days, and 1.45% at 365 days. The cumulative rates cited correct the crude rate (i.e., 0.7%, 25/3519) for the variable duration of exposure times among the patients who participated in the development program.

Although dose appears to be a predictor of seizure, there is a confounding of dose and duration of exposure, making it difficult to assess independently the effect of either factor alone. The ability to predict the occurrence of seizures in subjects exposed to doses of CMI greater than 250 mg is limited, given that the plasma concentration of CMI may be dose-dependent and may vary among subjects given the same dose. Nevertheless, prescribers are advised to limit the daily dose to a maximum of 250 mg for adults and 3 mg/kg (or 200 mg) in children and adolescents (see DOSAGE AND ADMINISTRATION).

Rare reports of fatalities in association with seizures have been recorded by foreign post-marketing surveillance systems over the 20 years of Anafranil's nondestructive marketing. In some of these cases, Anafranil had been administered with other epileptogenic agents; in others, the patients involved had possibly predisposing medical conditions.

Caution should be used in administering Anafranil to patients with a history of seizures or other predisposing factors, e.g., brain damage of varying etiology, alcoholism, and concomitant use with other drugs that lower the seizure threshold.

Physicians should discuss with patients the risk of taking Anafranil while engaging in activities in which sudden loss of consciousness could result in serious injury to the patient or others, e.g., the operation of complex machinery, driving, swimming, climbing.

#### PRECAUTIONS

##### General

**Suicide:** Since depression is a commonly associated feature of OCD, the risk of suicide must be considered. Prescriptions for Anafranil should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

**Cardiovascular Effects:** Modest orthostatic decreases in blood pressure and modest tachycardia were each seen in approximately 20% of patients taking Anafranil in clinical trials; but patients were frequently asymptomatic. Among approximately 1400 patients treated with CMI in the premarketing experience who had ECGs, 1.5% developed abnormalities during treatment, compared with 3.1% of patients receiving active control drugs and 0.7% of patients receiving placebo. The most common ECG changes were PVCs, ST-T wave changes, and intraventricular conduction abnormalities. These changes were rarely associated with significant clinical symptoms. Nevertheless, caution is necessary in treating patients with known cardiovascular disease, and gradual dose titration is recommended.

**Psychosis, Confusion, And Other Neuropsychiatric Phenomena:** Patients treated with Anafranil have been reported to show a variety of neuropsychiatric signs and symptoms including delusions, hallucinations, psychotic episodes, confusion, and paranoia. Because of the uncontrolled nature of many of the studies, it is impossible to provide a precise estimate of the extent of risk imposed by treatment with Anafranil. As with tricyclic antidepressants to which it is closely related, Anafranil may precipitate an acute psychotic episode in patients with unrecognized schizophrenia.

**Mania/Hypomania:** During premarketing testing of Anafranil in patients with affective disorder, hypomania or mania was precipitated in several patients. Activation of mania or hypomania has also been reported in a small proportion of patients with affective disorder treated with marketed tricyclic antidepressants, which are closely related to Anafranil.

**Hepatic Changes:** During premarketing testing, Anafranil was occasionally associated with elevations in SGOT and SGPT (pooled incidence of approximately 1% and 3%, respectively) of potential clinical importance (i.e., values greater than 3 times the upper limit of normal). In the vast majority of instances these enzyme increases were not associated with other clinical findings suggestive of hepatic injury; moreover, none were jaundiced. Rare reports of more severe liver injury, some fatal, have been recorded in foreign post-marketing experience. Caution is indicated in treating patients with known liver disease, and periodic monitoring of hepatic enzyme levels is recommended in such patients.

**Hematologic Changes:** Although no instances of severe hematologic toxicity were seen in the premarketing experience with Anafranil, there have been post-marketing reports of leukopenia, agranulocytosis, thrombocytopenia, anemia, and pancytopenia in association with Anafranil use. As is the case with tricyclic antidepressants to which Anafranil is closely related, leukocyte and differential blood counts should be obtained in patients who develop fever and sore throat during treatment with Anafranil.

**Central Nervous System:** More than 30 cases of hyperthermia have been recorded by nondestructive post-marketing surveillance systems. Most cases occurred when Anafranil was used in combination with other drugs when Anafranil and a neuroleptic were used concomitantly, the cases were sometimes considered to be examples of a neuroleptic malignant syndrome.

**Sexual Dysfunction:** The rate of sexual dysfunction in male patients with OCD who were treated with Anafranil in the premarketing experience was markedly increased compared with placebo controls (i.e., 42% experienced ejaculatory failure and 20% experienced impotence, compared with 2.0% and 2.6%, respectively, in the placebo group). Approximately 65% of males with sexual dysfunction chose to continue treatment.

**Weight Changes:** In controlled studies of OCD, weight gain was reported in 18% of patients receiving Anafranil, compared with 1% of patients receiving placebo. In these studies, 28% of patients receiving Anafranil had a weight gain of at least 7% of their initial body weight, compared with 4% of patients receiving placebo. Several patients had weight gains in excess of 25% of their initial body weight. Conversely, 5% of patients receiving Anafranil and 1% receiving placebo had weight losses of at least 7% of their initial body weight.

**Electroconvulsive Therapy:** As with closely related tricyclic antidepressants, concurrent administration of Anafranil with electroconvulsive therapy may increase the risks; such treatment should be limited to those patients for whom it is essential, since there is limited clinical experience.

**Surgery:** Prior to elective surgery with general anesthetics, therapy with Anafranil should be discontinued for as long as is clinically feasible, and the anesthesiologist should be advised.

**Use in Concomitant Illness:** As with closely related tricyclic antidepressants, Anafranil should be used with caution in the following:

1. Hyperthyroid patients or patients receiving thyroid medication, because of the possibility of cardiac toxicity.
2. Patients with increased intraocular pressure, a history of narrow-angle glaucoma, or urinary retention, because of the anticholinergic properties of the drug.
3. Patients with tumors of the adrenal medulla (e.g., pheochromocytoma, neuroblastoma) in whom the drug may provoke hypertensive crises.
4. Patients with significantly impaired renal function.

**Withdrawal Symptoms:** A variety of withdrawal symptoms have been reported in association with abrupt discontinuation of Anafranil, including dizziness, nausea, vomiting, headache, malaise, sleep disturbance, hyperthermia, and irritability. In addition, such patients may experience a worsening of psychiatric status. While the withdrawal effects of Anafranil have not been systematically evaluated in controlled trials, they are well known with closely related tricyclic antidepressants, and it is recommended that the dosage be tapered gradually and the patient monitored carefully during discontinuation (see DRUG ABUSE AND DEPENDENCE).

#### Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe Anafranil:

1. The risk of seizure (see WARNINGS).
2. The relatively high incidence of sexual dysfunction among males (see PRECAUTIONS, Sexual Dysfunction).
3. Since Anafranil may impair the mental and/or physical abilities required for the performance of complex tasks, and since Anafranil is associated with a risk of seizures, patients should be cautioned about the performance of complex and hazardous tasks (see WARNINGS).
4. Patients should be cautioned about using alcohol, barbiturates, or other CNS depressants concurrently, since Anafranil may exaggerate their response to these drugs.
5. Patients should notify their physician if they become pregnant or intend to become pregnant during therapy.
6. Patients should notify their physician if they are breast-feeding.

#### Drug Interactions

The risks of using Anafranil in combination with other drugs have not been systematically evaluated. Given the primary CNS effects of Anafranil, caution is advised in using it concomitantly with other CNS-active drugs (see PRECAUTIONS, Information for Patients). Anafranil should not be used with MAO inhibitors (see CONTRAINDICATIONS).

Close supervision and careful adjustment of dosage are required when Anafranil is administered with anticholinergic or sympathomimetic drugs.

Several tricyclic antidepressants have been reported to block the pharmacologic effects of guanethidine, clonidine, or similar agents, and such an effect may be anticipated with CMI because of its structural similarity to other tricyclic antidepressants.

The plasma concentration of CMI has been reported to be increased by the concomitant administration of haloperidol; plasma levels of several closely related tricyclic antidepressants have been reported to be increased by the concomitant administration of either methyphenidate, cimetidine, or fluoxetine and such an effect may be anticipated with CMI as well. Administration of CMI has been reported to increase the plasma levels of phenobarbital, if given concomitantly (see CLINICAL PHARMACOLOGY, Pharmacokinetic Interactions).

Because Anafranil is highly bound to serum protein, the administration of Anafranil to patients taking other drugs that are highly bound to protein (e.g., warfarin, digoxin) may cause an increase in plasma concentrations of these drugs, potentially resulting in adverse effects. Conversely, adverse effects may result from displacement of protein-bound Anafranil by other highly bound drugs (see CLINICAL PHARMACOLOGY, Distribution).

#### Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year bioassay, no clear evidence of carcinogenicity was found in rats given doses 20 times the maximum daily human dose. Three out of 235 treated rats had a rare (hemangioendothelioma); it is unknown if these neoplasms are compound related.

In reproduction studies, no effects on fertility were found in rats given doses approximately 5 times the maximum daily human dose.

#### Pregnancy Category C

No teratogenic effects were observed in studies performed in rats and mice at doses up to 20 times the maximum daily human dose. Slight nonspecific fetotoxic effects were seen in the offspring of pregnant mice given doses 10 times the maximum daily human dose. Slight nonspecific embryotoxicity was observed in rats given doses 5-10 times the maximum daily human dose.

There are no adequate or well-controlled studies in pregnant women. Withdrawal symptoms, including jitteriness, tremor, and seizures, have been reported in neonates whose mothers had taken Anafranil until delivery. Anafranil should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

#### Nursing Mothers

Anafranil has been found in human milk. Because of the potential for adverse reactions, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

#### Pediatric Use

In a controlled clinical trial in children and adolescents (10-17 years of age), 46 outpatients received Anafranil for up to 8 weeks. In addition, 150 adolescent patients have received Anafranil in open-label protocols for periods of several months to several years. Of the 196 adolescents studied, 50 were 13 years of age or less and 146 were 14-17 years of age. While the adverse reaction profile in this age group (see ADVERSE REACTIONS) is similar to that in adults, it is unknown what, if any, effects long-term treatment with Anafranil may have on the growth and development of children.

The safety and effectiveness in children below the age of 10 have not been established. Therefore, specific recommendations cannot be made for the use of Anafranil in children under the age of 10.

#### Use in Elderly

Anafranil has not been systematically studied in older patients; but 152 patients at least 60 years of age participating in U.S. clinical trials received Anafranil for periods of several months to several years. No unusual age-related adverse events have been identified in this elderly population, but these data are insufficient to rule out possible age-related differences, particularly in elderly patients who have concomitant systemic illnesses or who are receiving other drugs concomitantly.

#### ADVERSE REACTIONS

##### Commonly Observed

The most commonly observed adverse events associated with the use of Anafranil and not seen at an equivalent incidence among placebo-treated patients were gastrointestinal complaints, including dry mouth, constipation, nausea, dyspepsia, and anorexia; nervous system complaints, including somnolence, tremor, dizziness, nervousness, and myoclonus; genitourinary complaints, including changed libido, ejaculatory failure, impotence, and nocturnal disorder; and other miscellaneous complaints, including fatigue, sweating, increased appetite, weight gain, and visual changes.

##### Leading to Discontinuation of Treatment

Approximately 20% of 3616 patients who received Anafranil in U.S. premarketing clinical trials discontinued treatment because of an adverse event. Approximately one-half of the patients who discontinued (9% of the total) had multiple complaints, none of which could be classified as primary. Where a primary reason for discontinuation could be identified, most patients discontinued because of nervous system complaints (5.4%), primarily somnolence. The second-most frequent reason for discontinuation was digestive system complaints (1.3%), primarily vomiting and nausea.

##### Incidence in Controlled Clinical Trials

The following table enumerates adverse events that occurred at an incidence of 1% or greater among patients with OCD who received Anafranil in adult or pediatric placebo-controlled clinical trials. The frequencies were obtained from pooled data of clinical trials involving either adults receiving Anafranil (N = 322) or placebo (N = 319) or children treated with Anafranil (N = 46) or placebo (N = 44). The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice, in which patient characteristics and other factors differ from those which prevailed in the clinical trial. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, provide the physician with a basis for estimating the relative contribution of drug and nondrug factors to the incidence of side effects in the populations studied.

Incidence of Treatment-Emergent Adverse Experience  
in Placebo-Controlled Clinical Trials  
(Percentage of Patients Reporting)

Body System/ Adverse Event*	Adults		Children and Adolescents	
	Anafranil (N=322)	Placebo (N=319)	Anafranil (N=46)	Placebo (N=44)
Nervous System				
Somnolence	54	16	46	11
Tremor	54	2	33	2
Cinziness	54	14	41	14
Headache	52	41	28	34
Insomnia	25	15	11	7



## Anafanil® clomipramine hydrochloride

Body System/ Adverse Event *	Adults		Children and Adolescents	
	Anafanil (N=321)	Placebo (N=319)	Anafanil (N=46)	Placebo (N=44)
Lidido change	21	3	—	—
Nervousness	18	2	4	2
Myoclonus	13	—	2	—
Increased appetite	11	2	—	2
Paresthesia	9	3	7	—
Memory impairment	9	1	7	2
Anxiety	9	4	2	—
Twitching	7	1	4	5
Impaired concentration	5	2	—	—
Depression	5	1	—	—
Hypertonia	4	1	2	—
Sleep disorder	4	—	9	5
Psychosomatic disorder	3	—	—	—
Yawning	3	—	—	—
Confusion	3	—	2	—
Speech disorder	3	—	—	—
Abnormal dreaming	3	—	2	—
Agitation	3	—	—	—
Migraine	3	—	—	—
Depersonalization	2	—	2	—
Irritability	2	2	—	2
Emotional lability	2	—	2	—
Panic reaction	1	—	2	—
Aggressive reaction	—	—	2	—
Paresis	—	—	2	—
Skin and Appendages				
Increased sweating	29	3	9	—
Rash	8	1	4	2
Pruritus	6	—	2	—
Dermatitis	2	—	2	—
Acne	2	2	—	5
Dry skin	2	—	—	—
Urticaria	1	—	—	—
Abnormal skin odor	—	—	2	—
Digestive System				
Dry mouth	84	17	63	16
Constipation	47	11	22	9
Nausea	33	14	9	11
Dyspepsia	22	10	13	2
Diarrhea	13	9	7	5
Anorexia	12	—	22	2
Abdominal pain	11	9	13	16
Vomiting	7	2	7	—
Flatulence	6	3	—	2
Tooth disorder	5	—	—	—
Gastrointestinal disorder	2	—	—	2
Dysphagia	2	—	—	—
Esophagitis	1	—	—	—
Eruetion	—	—	2	2
Ulcerative stomatitis	—	—	2	—
Body as a Whole				
Fatigue	39	18	35	9
Weight increase	18	1	2	—
Flushing	8	—	7	—
Hot flushes	5	—	2	—
Chest pain	4	4	7	—
Fever	4	—	2	7
Allergy	3	3	7	4
Pain	3	2	4	2
Local edema	2	—	—	—
Chills	2	1	—	—
Weight decrease	—	—	—	—
Otitis media	—	—	4	5
Asthenia	—	—	2	—
Halitosis	—	—	2	—
Cardiovascular System				
Postural hypotension	6	—	4	—
Palpitation	4	2	4	—
Tachycardia	4	—	2	—
Syncope	—	—	2	—
Respiratory System				
Pharyngitis	14	9	—	5
Rhinitis	12	10	7	9
Sinusitis	6	4	2	—
Coughing	6	6	4	5
Bronchospasm	2	—	7	2
Epistaxis	2	—	—	2
Dyspnea	—	—	2	—
Laryngitis	—	1	2	—
Urogenital System				
Male and Female Patients Combined				
Micturition disorder	14	2	4	2
Urinary tract infection	6	1	—	—
Micturition frequency	5	3	—	—
Urinary retention	2	—	7	—
Dysuria	2	2	—	—
Cystitis	2	—	—	—
Female Patients Only	(N=182)	(N=167)	(N=10)	(N=21)
Dysmenorrhea	12	14	10	10
Lactation (nonpuerperal)	4	—	—	—
Menstrual disorder	4	2	—	—
Vaginitis	2	—	—	—
Leukorrhea	2	—	—	—
Breast enlargement	2	—	—	—
Breast pain	1	—	—	—
Amenorrhea	1	—	—	—
Male Patients Only	(N=140)	(N=152)	(N=36)	(N=23)
Ejaculation failure	42	2	6	—
Impotence	20	3	—	—
Special Senses				
Abnormal vision	18	4	7	2
Taste perversion	8	—	4	—
Tinnitus	6	—	4	—
Abnormal lacrimation	3	2	—	—
Mydriasis	2	—	—	—
Conjunctivitis	1	—	—	—
Anisocoria	—	—	2	—
Blepharospasm	—	—	2	—
Ocular allergy	—	—	2	—
Vestibular disorder	—	—	2	2
Musculoskeletal				
Myalgia	13	9	—	—
Back pain	6	—	—	—
Arthralgia	3	5	—	—
Muscle weakness	1	—	2	—
Hemic and Lymphatic				
Purpura	3	—	—	—
Anemia	—	—	2	2
Metabolic and Nutritional				
Thirst	2	2	—	2

## Other Events Observed During the Premarketing Evaluation of Anafanil

During clinical testing in the U.S., multiple doses of Anafanil were administered to approximately 3600 subjects. Unwanted events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of unwanted events into a smaller number of standardized event categories.

In the tabulations that follow, a modified World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the 3525 individuals exposed to Anafanil who experienced an event of the type cited on at least one occasion while receiving Anafanil. All events are included except those already listed in the previous table, those reported in terms so general as to be uninformative, and those in which an association with the drug was remote. It is important to emphasize that although the events reported occurred during treatment with Anafanil, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in less than 1/1000 patients.

**Body as a Whole:** Infrequent — general edema, increased susceptibility to infection, malaise. Rare — dependent edema, withdrawal syndrome.

**Cardiovascular System:** Infrequent — abnormal ECG, arrhythmia, bradycardia, cardiac arrest, extrasystoles, pallor. Rare — aneurysm, atrial flutter, bundle branch block, cardiac failure, cerebral hemorrhage, heart block, myocardial infarction, myocardial ischemia, peripheral ischemia, thrombophlebitis, vasospasm, ventricular tachycardia.

**Digestive System:** Infrequent — abnormal hepatic function, blood in stool, colitis, duodenitis, gastric ulcer, gastritis, gastroesophageal reflux, gingivitis, glossitis, hemorrhoids, hepatitis, increased saliva, irritable bowel syndrome, peptic ulcer, rectal hemorrhage, tongue ulceration, tooth caries. Rare — cheilitis, chronic enteritis, discoloration of feces, gastric dilatation, gingival bleeding, hiccup, intestinal obstruction, oral/pharyngeal edema, paralytic ileus, salivary gland enlargement.

**Endocrine System:** Infrequent — hypothyroidism. Rare — goiter, gynecomastia, hyperthyroidism.

**Hemic and Lymphatic System:** Infrequent — lymphadenopathy. Rare — leukemoid reaction, lymphoma-like disorder, marrow depression.

**Metabolic and Nutritional Disorders:** Infrequent — dehydration, diabetes mellitus, gout, hypercholesterolemia, hyperglycemia, hyperuricemia, hypokalemia. Rare — fat intolerance, glycosuria.

**Musculoskeletal System:** Infrequent — arthrosis. Rare — dystonia, exostosis, lupus erythematosus rash, bruising, myopathy, myositis, polyarthritis nodosa, torticollis.

**Nervous System:** Frequent — abnormal thinking, vertigo. Infrequent — abnormal coordination, abnormal EEG, abnormal gait, apathy, ataxia, coma, convulsions, delirium, delusion, dyskinesia, dysphonia, encephalopathy, euphoria, extrapyramidal disorder, hallucinations, hostility, hyperkinesia, hypnagogic hallucinations, hypokinesia, leg cramps, manic reaction, neuralgia, paranoia, phobic disorder, psychosis, sensory disturbance, somnambulism, stimulation, suicidal ideation, suicide attempt, teeth-grinding. Rare — anticholinergic syndrome, aphasia, apraxia, cataplexy, cholinergic syndrome, choreoathetosis, generalized spasm, hemiparesis, hyperesthesia, hyperreflexia, hyposthesia, illusion, impaired impulse control, incoherence, mutism, neuropathy, nystagmus, oculogyric crisis, oculomotor nerve paralysis, schizophrenic reaction, stupor, suicide.

**Respiratory System:** Infrequent — bronchitis, hyperventilation, increased sputum, pneumonia. Rare — cyanosis, hemoptysis, hypopentilation, laryngismus.

**Skin and Appendages:** Infrequent — alopecia, cellulitis, cyst, eczema, erythematous rash, genital pruritus, maculopapular rash, photosensitivity reaction, psoriasis, pustular rash, skin discoloration. Rare — chloasma, folliculitis, hypertrichosis, pilorection, seborrhea, skin hypertrophy, skin ulceration.

**Special Senses:** Infrequent — abnormal accommodation, deafness, diplopia, earache, eye pain, foreign body sensation, hyperacusis, parosmia, photophobia, scleritis, taste loss. Rare — blepharitis, chromatopsia, conjunctival hemorrhage, exophthalmos, glaucoma, keratitis, labyrinth disorder, night blindness, retinal disorder, strabismus, visual field defect.

**Urogenital System:** Infrequent — endometriosis, epididymitis, hematuria, nocturia, oliguria, ovarian cyst, perineal pain, polyuria, prostatic disorder, renal calculus, renal pain, testis disorder, urethral disorder, urinary incontinence, uterine hemorrhage, vaginal hemorrhage. Rare — albuminuria, anorgasm, breast engorgement, breast fibroadenosis, cervical dysplasia, endometrial hyperplasia, premature ejaculation, pyelonephritis, pyuria, renal cyst, uterine inflammation, vulvar disorder.

## DRUG ABUSE AND DEPENDENCE

Anafanil has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. While a variety of withdrawal symptoms have been described in association with Anafanil discontinuation (see PRECAUTIONS, Withdrawal Symptoms), there is no evidence for drug-seeking behavior, except for a single report of potential Anafanil abuse by a patient with a history of dependence on cocaine, benzodiazepines, and multiple psychoactive drugs. The patient received Anafanil for depression and panic attacks and appeared to become dependent after hospital discharge.

Despite the lack of evidence suggesting an abuse liability for Anafanil in foreign marketing, it is not possible to predict the extent to which Anafanil might be misused or abused once marketed in the U.S. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely.

## OVERDOSAGE

## Human Experience

In U.S. clinical trials, 2 deaths occurred in 12 reported cases of acute overdosage with Anafanil either alone or in combination with other drugs. One death involved a patient suspected of ingesting a dose of 7000 mg. The second death involved a patient suspected of ingesting a dose of 5750 mg. The 10 nonfatal cases involved doses of up to 5000 mg, accompanied by plasma levels of up to 1010 ng/ml. All 10 patients completely recovered. Among reports from other countries of Anafanil overdosage, the lowest dose associated with a fatality was 750 mg. Based upon post-marketing reports in the United Kingdom, CMI's lethality in overdosage is considered to be similar to that reported for closely related tricyclic compounds marketed as antidepressants.

## Signs and Symptoms

Signs and symptoms vary in severity depending upon factors such as the amount of drug absorbed, the age of the patient, and the time elapsed since drug ingestion. Blood and urine levels of Anafanil may not reflect the severity of poisoning; they have chiefly a qualitative rather than quantitative value, and they are unreliable indicators in the clinical management of the patient. The first signs and symptoms of poisoning with tricyclic antidepressants are generally severe anticholinergic reactions. CNS abnormalities may include drowsiness, stupor, coma, ataxia, restlessness, agitation, delirium, severe perspiration, hyperactive reflexes, muscle rigidity, atetoid and choreiform movements, and convulsions. Cardiac abnormalities may include arrhythmia, tachycardia, ECG evidence of impaired conduction, and signs of congestive heart failure, and in very rare cases, cardiac arrest. Respiratory depression, cyanosis, hypotension, shock, vomiting, hyperpyrexia, mydriasis, oliguria or anuria, and diaphoresis may also be present.

## Treatment

The recommended treatment for tricyclic overdose may change periodically. Therefore, it is recommended that the physician contact a poison control center for current information on treatment.

Because CNS involvement, respiratory depression, and cardiac arrhythmia can occur suddenly, hospitalization and close observation are necessary, even when the amount ingested is thought to be small or the initial degree of intoxication appears slight or moderate. All patients with ECG abnormalities should have continuous cardiac monitoring for at least 72 hours and be closely observed until well after the cardiac status has returned to normal; relapses may occur after apparent recovery. The slow intravenous administration of physostigmine

salicylate has been reported to reverse the cardiovascular and CNS anticholinergic manifestations of tricyclic overdosage; however, it should not be used routinely, since it may induce seizures and cholinergic crises and there is persisting debate about its net utility.

In the alert patient, the stomach should be emptied promptly by induced emesis followed by lavage. In the obtunded patient, the airway should be secured with a cuffed endotracheal tube before beginning lavage (do not induce emesis). Lavage should be continued for 24 hours or longer, depending on the apparent severity of intoxication. Normal or half-normal saline should be used to avoid water intoxication, especially in children. Instillation of activated charcoal slurry may help reduce absorption of CMI.

External stimulation should be minimized to reduce the tendency for convulsions, and anticonvulsants may be necessary. If MAO inhibitors have been taken recently, barbiturates should not be used. Adequate respiratory exchange should be maintained, including intubation and artificial respiration, if necessary. Respiratory stimulants should not be used.

In severe hypotension or shock, the patient should be placed in an appropriate position and given a plasma expander, dopamine, or dobutamine by intravenous drip. The use of corticosteroids in shock is controversial and may be contraindicated in cases of overdosage with tricyclic antidepressants. Digitalis may increase conduction abnormalities and further irritate an already sensitized myocardium. If congestive heart failure necessitates rapid digitalization, particular care must be exercised. Hyperpyrexia should be controlled by whatever external means are available, including ice packs and cooling sponge baths, if necessary. Hemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis have generally been reported as ineffective because of the rapid fixation of Anafanil in tissues.

## DOSAGE AND ADMINISTRATION

The treatment regimens described below are based on those used in controlled clinical trials of Anafanil in 520 adults, and 91 children and adolescents with OCD. During initial titration, Anafanil should be given in divided doses with meals to reduce gastrointestinal side effects. The goal of this initial titration phase is to minimize side effects by permitting tolerance to side effects to develop or allowing the patient time to adapt if tolerance does not develop.

Because both CMI and its active metabolite, DMI, have long elimination half-lives, the prescriber should take into consideration the fact that steady-state plasma levels may not be achieved until 2-3 weeks after dosage change (see CLINICAL PHARMACOLOGY). Therefore, after initial titration, it may be appropriate to wait 2-3 weeks between further dosage adjustments.

## Initial Treatment/Dose Adjustment (Adults)

Treatment with Anafanil should be initiated at a dosage of 25 mg daily and gradually increased, as tolerated, to approximately 100 mg during the first 2 weeks. During initial titration, Anafanil should be given in divided doses with meals to reduce gastrointestinal side effects. Thereafter, the dosage may be increased gradually over the next several weeks, up to a maximum of 250 mg daily. After titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation.

## Initial Treatment/Dose Adjustment (Children and Adolescents)

As with adults, the starting dose is 25 mg daily and should be gradually increased (also given in divided doses with meals to reduce gastrointestinal side effects) during the first 2 weeks, as tolerated, up to a daily maximum of 3 mg/kg or 100 mg, whichever is smaller. Thereafter, the dosage may be increased gradually over the next several weeks up to a daily maximum of 3 mg/kg or 200 mg, whichever is smaller (see PRECAUTIONS, Pediatric Use). As with adults, after titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation.

## Maintenance/Continuation Treatment (Adults, Children, and Adolescents)

While there are no systematic studies that answer the question of how long to continue Anafanil, OCD is a chronic condition and it is reasonable to consider continuation for a responding patient. Although the efficacy of Anafanil after 10 weeks has not been documented in controlled trials, patients have been continued in therapy under double-blind conditions for up to 1 year without loss of benefit. However, dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for treatment. During maintenance, the total daily dose may be given once daily at bedtime.

## HOW SUPPLIED

**Capsules 25 mg** — ivory/melon yellow (imprinted ANAFANIL 25 mg)  
Bottles of 100 ..... NDC 0083-0115-30  
Unit Dose (blister pack)  
Box of 100 (strips of 10) ..... NDC 0083-0115-32  
**Capsules 50 mg** — ivory/aqua blue (imprinted ANAFANIL 50 mg)  
Bottles of 100 ..... NDC 0083-0116-30  
Unit Dose (blister pack)  
Box of 100 (strips of 10) ..... NDC 0083-0116-32  
**Capsules 75 mg** — ivory/yellow (imprinted ANAFANIL 75 mg)  
Bottles of 100 ..... NDC 0083-0117-30  
Unit Dose (blister pack)  
Box of 100 (strips of 10) ..... NDC 0083-0117-32

Do not store above 86°F (30°C). Protect from moisture.

Dispense in tight container (USP).

## ANIMAL TOXICOLOGY

Testicular and lung changes commonly associated with tricyclic compounds have been observed with Anafanil. In 1- and 2-year studies in rats, changes in the testes (atrophy, aspermatogenesis, and calcification) and drug-induced phospholipidosis in the lungs were observed at doses 4 times the maximum daily human dose. Testicular atrophy was also observed in a 1-year oral toxicity study in dogs at 10 times the maximum daily human dose.

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C I B A

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Summit, New Jersey 07901

\* Events reported by at least 1% of Anafanil patients are included

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*Coming in the May 1990 issue of*

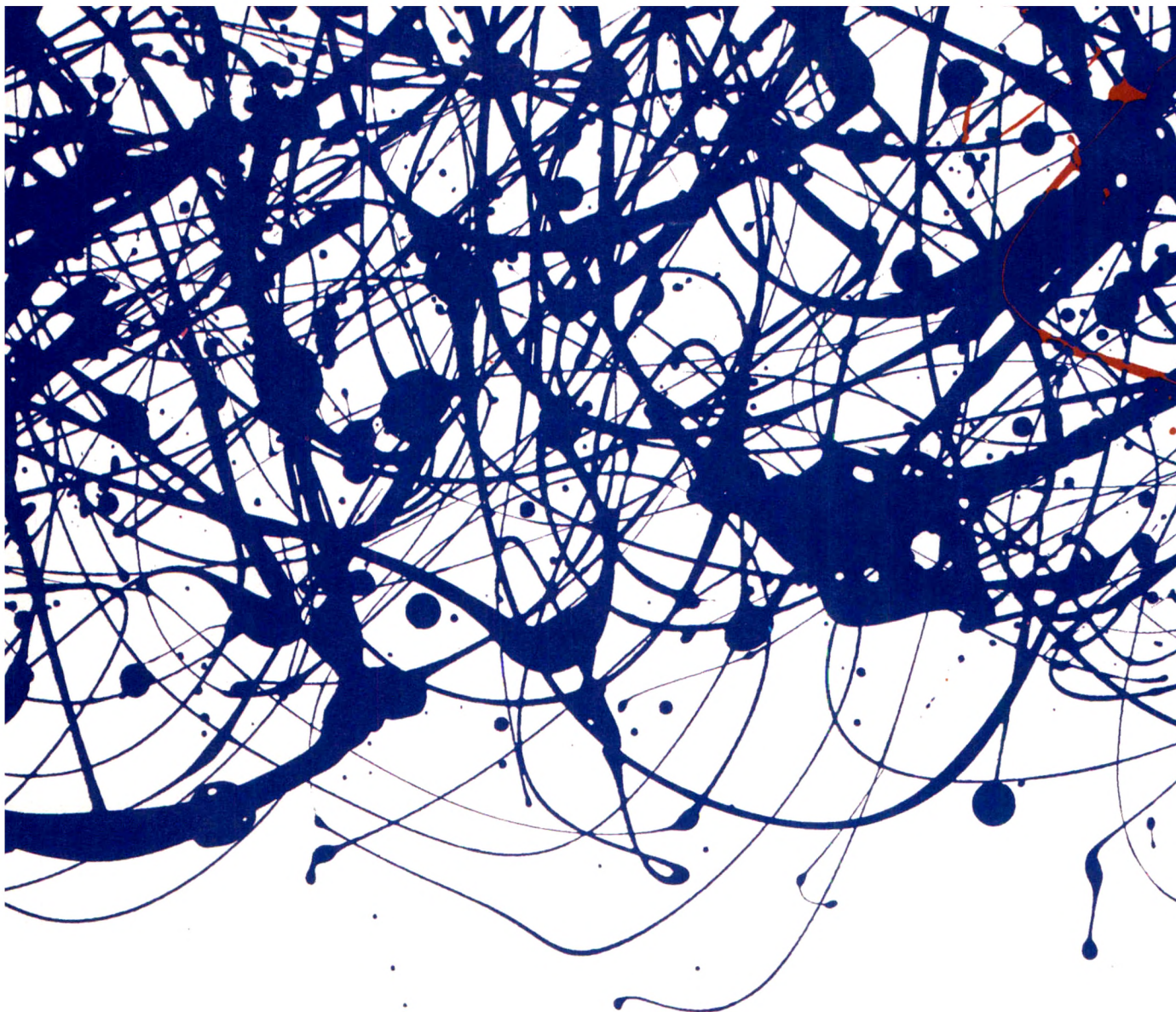
## THE AMERICAN JOURNAL OF PSYCHIATRY

*Cults and Zealous Self-Help Movements: A Psychiatric Perspective*  
By Marc Galanter

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Does Antidepressant Response Identify a Family  
of Disorders With a Common Pathophysiology?*  
By James I. Hudson and Harrison G. Pope, Jr.

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# With depression..

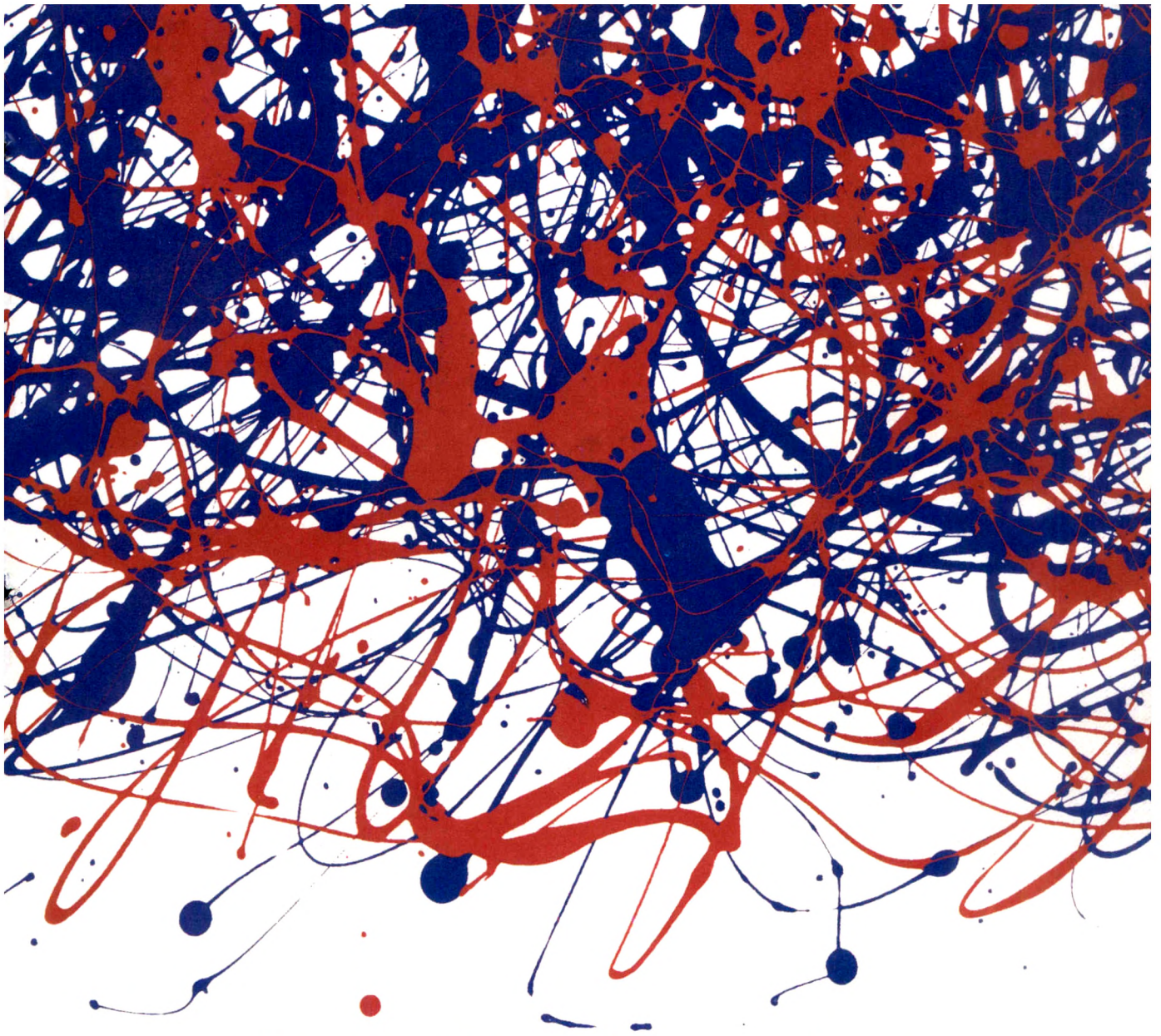
In a clinical trial, XANAX was effective in reducing anxiety symptoms associated with moderate to severe depression.\*

Patients taking XANAX should be alerted to possible additive CNS depressant effects when it is administered with other medications that produce CNS depression.

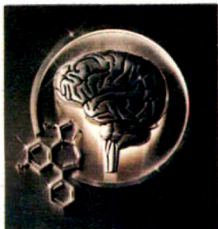
The usual starting dosage of XANAX is 0.25 to 0.5 mg t.i.d.

\*Data on file. The Upjohn Company





**you often find anxiety**



TABLETS 0.5 MG  
**Xanax**<sup>®</sup>  
alprazolam<sup>®</sup>

**For anxiety associated with  
depression**

**Upjohn**

Please see adjacent page for brief summary of prescribing information.

The Upjohn Company  
Kalamazoo, Michigan 49001, USA

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**XANAX® Tablets**  
(alprazolam, ©)

#### INDICATIONS AND USAGE

Anxiety disorders, short-term relief of the symptoms of anxiety, and anxiety associated with depression. Anxiety or tension associated with the stress of everyday life usually does not require an anxiolytic. Effectiveness for more than four months has not been established; periodically reassess the usefulness of the drug for the individual patient.

#### CONTRAINDICATIONS

Sensitivity to XANAX or other benzodiazepines, and in acute narrow angle glaucoma.

#### WARNINGS

XANAX is not of value in treating psychosis and should not be used in lieu of appropriate treatment. Patients receiving XANAX should be cautioned about hazardous occupations or activities requiring full alertness and also about simultaneous ingestion of alcohol or other CNS depressants.

Benzodiazepines can cause fetal harm in pregnant women, hence women who may become pregnant should be warned. Avoid during the first trimester. Withdrawal seizures have been reported upon rapid dose reduction or abrupt discontinuation, thus reduce dose gradually. (See Drug Abuse and Dependence and Dosage and Administration.)

#### PRECAUTIONS

**General:** If XANAX is combined with other psychotropics or anticonvulsants, consider drug potentiation. (See Drug Interactions.) Use the usual precautions in patients with renal or hepatic impairment and regarding prescription size in depressed and suicidal patients. In elderly and debilitated patients, use the lowest possible dose. (See Dosage and Administration.) Hypomania and mania has been reported in depressed patients.

**Information for Patients:** Alert patients about: (a) consumption of alcohol and drugs; (b) possible fetal abnormalities; (c) operating machinery or driving; (d) not increasing dose of the drug due to risk of dependence; (e) not stopping the drug abruptly. **Laboratory Tests:** Not ordinarily required in otherwise healthy patients. **Drug Interactions:** Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Plasma levels of imipramine and desipramine are increased. Pharmacokinetic interactions with other drugs have been reported. Cimetidine can delay clearance of benzodiazepines. **Drug/Laboratory Test Interactions:** No consistent pattern for a drug or test. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** No carcinogenic potential or impairment of fertility in rats. **Pregnancy:** See Warnings. **Nonteratogenic Effects:** The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms, neonatal flaccidity and respiratory problems. **Labor and Delivery:** No established use. **Nursing Mothers:** Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. **Pediatric Use:** Safety and effectiveness in children below the age of 18 have not been established.

#### ADVERSE REACTIONS

Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

**Central nervous system:** Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. **Gastrointestinal:** Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. **Cardiovascular:** Tachycardia/palpitations, and hypotension. **Sensory:** Blurred vision. **Musculoskeletal:** Rigidity and tremor. **Cutaneous:** Dermatitis/allergy. **Other side effects:** Nasal congestion, weight gain, and weight loss.

Withdrawal seizures with rapid decrease or abrupt discontinuation. (See Warnings.)

The following adverse events have been reported with benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, seizures, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence, and urinary retention.

Paradoxical reactions such as stimulation, agitation, rage, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

Liver enzyme elevations, gynecomastia and galactorrhea have been reported but no causal relationship was established.

#### DRUG ABUSE AND DEPENDENCE

**Physical and Psychological Dependence:** Withdrawal symptoms including seizures have occurred following abrupt discontinuance or rapid dose reduction of benzodiazepines. (See Warnings.) Dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. **Controlled Substance Class:** XANAX is a controlled substance and has been assigned to schedule IV.

#### OVERDOSAGE

Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

#### DOSAGE AND ADMINISTRATION

Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 mg every three days.

#### HOW SUPPLIED

XANAX Tablets are available as 0.25 mg, 0.5 mg, and 1 mg tablets.

**CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.**

**Upjohn** THE UPJOHN COMPANY  
Kalamazoo, Michigan 49001, USA

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November, 1989

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**I didn't know  
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**Avoid confusion...  
always specify**

**Stelazine<sup>®</sup>**  
brand of  
trifluoperazine HCl

**Available in Tablets: 1, 2, 5 and 10 mg  
Multiple-dose Vials: 10 mL (2 mg/mL)  
Concentrate: 10 mg/mL**

**Before prescribing, please see brief summary of  
prescribing information on adjacent page.**

**SK&F LAB CO.**



# Stelazine®

brand of  
trifluoperazine HCl

**Before prescribing, see complete prescribing information in SK&F Lab Co. literature or PDR. The following is a brief summary.**

**Contraindications:** Comatose or greatly depressed states due to C.N.S. depressants, blood dyscrasias; bone marrow depression; liver damage.

**Warnings:** Tardive dyskinesia (TD) may develop in patients treated with neuroleptic (antipsychotic) drugs. The risk of TD and likelihood of irreversibility are thought to increase as duration of treatment and total cumulative neuroleptic dose increase. Much less commonly, the syndrome can develop after relatively brief treatment at low doses. There is no known treatment for TD, although it may remit if neuroleptics are withdrawn. Neuroleptic treatment may suppress signs and symptoms of the syndrome and thereby mask the underlying disease process. To minimize risk of TD, generally reserve chronic neuroleptic treatment for patients who suffer from chronic illness that responds to neuroleptics and for whom alternative, effective, less harmful treatments are not available or appropriate. In patients requiring chronic treatment, the minimal effective dose and shortest duration of treatment should be sought. Periodically reassess need for continued treatment. If signs and symptoms of TD appear, discontinuation of neuroleptics should be considered. (See PRECAUTIONS.)

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported in association with antipsychotic drugs. Clinical manifestations include: Hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment, if available, of any concomitant serious medical problems.

'Stelazine' Concentrate contains sodium bisulfite, which may cause allergic-type reactions including anaphylactic symptoms or asthmatic episodes in certain susceptible people. The prevalence of sulfite sensitivity in the general population is unknown and probably low and is seen more frequently in asthmatic than in non-asthmatic people.

Generally avoid using in patients hypersensitive (e.g., have had blood dyscrasias, jaundice) to any phenothiazine. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery), especially during the first few days' therapy. Additive depressant effect is possible with other C.N.S. depressants, including alcohol. Do not use in pregnancy except when essential and potential benefits clearly outweigh possible hazards. Prolonged jaundice, extrapyramidal signs, hyperreflexia and hyporeflexia have been reported in newborns whose mothers received phenothiazines. There is evidence that phenothiazines are excreted in the breast milk of nursing mothers.

**Precautions:** Since some patients chronically exposed to neuroleptics will develop tardive dyskinesia, it is advised that, if possible, full information about this risk be given to patients or their guardians when chronic use is contemplated.

Use cautiously in angina. Avoid high doses and parenteral use when cardiovascular system is impaired since hypotension has occurred. Antiemetic effect may mask the signs of overdosage of other drugs or obscure diagnosis and treatment of certain physical disorders. Prolonged use of high doses may result in cumulative effects with severe C.N.S. or vasomotor symptoms. If retinal changes occur, discontinue drug. Agranulocytosis, thrombocytopenia, pancytopenia, anemia, cholestatic jaundice, liver damage have been reported. Use cautiously in patients with glaucoma.

Patients with a history of long-term therapy with 'Stelazine' and/or other neuroleptics should be evaluated periodically for possible dosage adjustment or discontinuance of drug therapy. Neuroleptic drugs cause elevated prolactin levels that persist during chronic use. Since approximately one-third of human breast cancers are prolactin-dependent *in vitro*, this elevation is of potential importance if neuroleptic drug use is contemplated in a patient with a previously detected breast cancer. However, clinical and epidemiologic studies to date have not shown an association between the chronic use of neuroleptic drugs and mammary tumorigenesis. Chromosomal aberrations in spermatocytes and abnormal sperm have been demonstrated in rodents treated with certain neuroleptics. Use cautiously in persons who will be exposed to extreme heat.

Phenothiazines may diminish the effect of oral anticoagulants. Phenothiazines can produce alpha-adrenergic blockade. Concomitant use of phenothiazines with propranolol increases plasma levels of both drugs. Concurrent use of phenothiazines may counteract antihypertensive effects of guanethidine and related compounds. Thiazide diuretics may accentuate the orthostatic hypotension that may occur with phenothiazines. Phenothiazines may lower the convulsive threshold and may also precipitate phenytoin toxicity; dosage adjustments of anticonvulsants may be necessary. If neuromuscular reactions occur in pregnant women, or in children, permanently stop neuroleptic therapy. Patients should not receive 'Stelazine' 48 hours before or 24 hours after myelography with the contrast medium metrizamide. The presence of phenothiazines may produce false positive phenylketonuria (PKU) test results.

**Adverse Reactions:** Drowsiness, dizziness, skin reactions, rash, dry mouth, insomnia, amenorrhea, fatigue, muscular weakness, anorexia, lactation, blurred vision. Neuromuscular (extrapyramidal) reactions: motor restlessness, dystonias, pseudo-parkinsonism, tardive dyskinesia, and a variant, tardive dystonia.

**Other adverse reactions reported with Stelazine (trifluoperazine HCl, SK&F) or other phenothiazines:** Some adverse effects are more frequent or intense in specific disorders (e.g., mitral insufficiency or pheochromocytoma).

Grand mal and petit mal convulsions, particularly in the presence, or with history, of EEG abnormalities; altered cerebrospinal fluid proteins; cerebral edema; prolongation and intensification of the action of C.N.S. depressants, atropine, heat, and organophosphorus insecticides; nasal congestion, headache, nausea, constipation, obstipation, adynamic ileus, ejaculatory disorders/impotence, priapism, atonic colon, urinary retention, miosis and mydriasis; reactivation of psychotic processes, catatonic-like states, hypotension (sometimes fatal); cardiac arrest; leukopenia, eosinophilia, pancytopenia, agranulocytosis, thrombocytopenic purpura, hemolytic anemia, aplastic anemia, jaundice, biliary stasis, hyperglycemia, hypoglycemia, glycosuria, menstrual irregularities, galactorrhea, gynecomastia, false positive pregnancy tests, photosensitivity, itching, erythema, urticaria, eczema up to exfoliative dermatitis, asthma, laryngeal edema, angioneurotic edema, anaphylactoid reactions, peripheral edema; reversed epinephrine effect; hyperpyrexia; mild fever after large I.M. doses; increased appetite; increased weight; a systemic lupus erythematosus-like syndrome; pigmentary retinopathy; with prolonged administration of substantial doses, skin pigmentation, epithelial keratopathy, and lenticular and corneal deposits; neuroleptic malignant syndrome, which may be fatal; EKG changes—particularly nonspecific, usually reversible Q and T wave distortions—have been observed. Temporary nausea, vomiting, dizziness, and tremulousness may follow abrupt cessation of high-dose therapy. NOTE: Sudden death in patients taking phenothiazines (apparently due to cardiac arrest or asphyxia due to failure of cough reflex) has been reported.

## SK&F LAB CO.

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SK&F Lab Co., Cidra, P.R. 00639

BRS-SZ:L64

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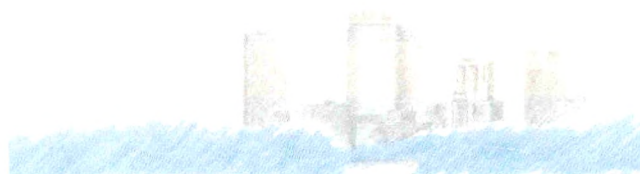
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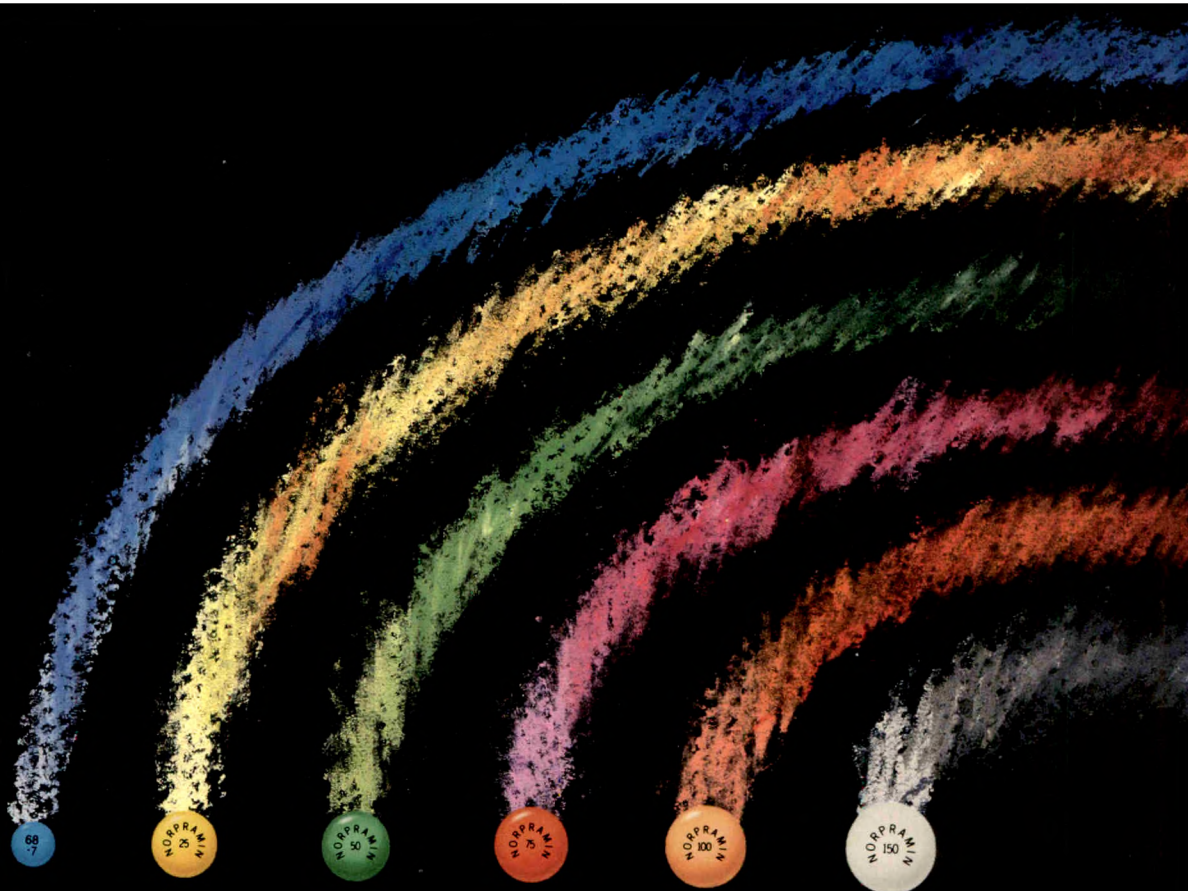
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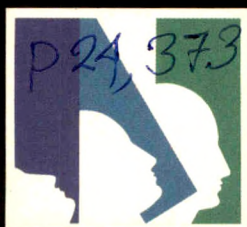
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A logical choice among antidepressants

**A 25-year history** of proven clinical usefulness with unsurpassed **flexibility of dosage** provided by 6 tablet strengths, **color coded** to ensure exact identification. It also offers **dose equivalence** that permits prescribing one tablet of greater strength in place of multiple doses of lesser strengths, resulting in **increased patient compliance** and greater than **20% cost savings**.

(Brief Summary of Prescribing Information appears on the next page.)





**Ensure the maximum benefits of Norpramin by specifying "Dispense As Written."**

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\*References supporting these statements available from MERRELL DOW PHARMACEUTICALS INC., Cincinnati, Ohio 45242.

†Norpramin does not usually inhibit normal activity, although patients should be cautioned against driving or operating machinery if drowsiness occurs (see Warnings, Precautions, and Adverse Reactions).

# Norpramin®

10, 25, 50, 75, 100, 150 mg  
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## Norpramin® (desipramine hydrochloride tablets USP)

### BRIEF SUMMARY

**CAUTION:** Federal law prohibits dispensing without prescription.

### INACTIVE INGREDIENTS

The following inactive ingredients are contained in all dosage strengths: acacia, calcium carbonate, corn starch, D&C Red No. 30 and D&C Yellow No. 10 (except 10 mg and 150 mg), FD&C Blue No. 1, FD&C Red No. 3, FD&C Yellow No. 6, hydrogenated soy oil, iron oxide, light mineral oil, magnesium stearate, mannitol, polyethylene glycol 8000, pregelatinized corn starch, sodium benzoate (except 150 mg), sucrose, talc, titanium dioxide, and other ingredients.

### CLINICAL PHARMACOLOGY

#### Metabolism

The rate of metabolism of tricyclic antidepressants varies widely from individual to individual, chiefly on a genetically determined basis. In general, the elderly metabolize tricyclic antidepressants more slowly than do younger adults.

Certain drugs, particularly the psychostimulants and the phenothiazines, increase plasma levels of concomitantly administered tricyclic antidepressants through competition for the same metabolic enzyme systems. Other substances, particularly barbiturates and alcohol, induce liver enzyme activity and thereby reduce tricyclic antidepressant plasma levels. Similar effects have been reported with tobacco smoke.

Additional information on metabolism appears in Full Prescribing Information.

### CONTRAINDICATIONS

Desipramine hydrochloride should not be given in conjunction with, or within 2 weeks of, treatment with an MAO inhibitor drug; hyperpyretic crises, severe convulsions, and death have occurred in patients taking MAO inhibitors and tricyclic antidepressants. When Norpramin (desipramine hydrochloride) is substituted for an MAO inhibitor, at least 2 weeks should elapse between treatments. Norpramin should then be started cautiously and should be increased gradually.

The drug is contraindicated in the acute recovery period following myocardial infarction. It should not be used in those who have shown prior hypersensitivity to the drug. Cross sensitivity between this and other dibenzazepines is a possibility.

### WARNINGS

- Extreme caution should be used when this drug is given in the following situations:
  - In patients with cardiovascular disease, because of the possibility of conduction defects, arrhythmias, tachycardias, strokes, and acute myocardial infarction.
  - In patients with a history of urinary retention or glaucoma, because of the anticholinergic properties of the drug.
  - In patients with thyroid disease or those taking thyroid medication, because of the possibility of cardiovascular toxicity, including arrhythmias.
  - In patients with a history of seizure disorder, because this drug has been shown to lower the seizure threshold.
- This drug is capable of blocking the antihypertensive effect of guanethidine and similarly acting compounds.
- USE IN PREGNANCY**  
Safe use of desipramine hydrochloride during pregnancy and lactation has not been established; therefore, if it is to be given to pregnant patients, nursing mothers, or women of childbearing potential, the possible benefits must be weighed against the possible hazards to mother and child. Animal reproductive studies have been inconclusive.
- USE IN CHILDREN**  
Norpramin (desipramine hydrochloride) is not recommended for use in children since safety and effectiveness in the pediatric age group have not been established. (See ADVERSE REACTIONS, Cardiovascular.)
- The patient should be cautioned that this drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.
- In patients who may use alcohol excessively, it should be borne in mind that the potentiation may increase the danger inherent in any suicide attempt or overdose.

### PRECAUTIONS

- It is important that this drug be dispensed in the least possible quantities to depressed outpatients, since suicide has been accomplished with this class of drug. Ordinary prudence requires that children not have access to this drug or to potent drugs of any kind; if possible, this drug should be dispensed in containers with child-resistant safety closures. Storage of this drug in the home must be supervised responsibly.
- If serious adverse effects occur, dosage should be reduced or treatment should be altered.
- Norpramin (desipramine hydrochloride) therapy in patients with manic-depressive illness may induce a hypomanic state after the depressive phase terminates.
- The drug may cause exacerbation of psychosis in schizophrenic patients.
- Close supervision and careful adjustment of dosage are required when this drug is given concomitantly with anticholinergic or sympathomimetic drugs.
- Patients should be warned that while taking this drug their response to alcoholic beverages may be exaggerated.
- Clinical experience in the concurrent administration of ECT and antidepressant drugs is limited. Thus, if such treatment is essential, the possibility of increased risk relative to benefits should be considered.
- If Norpramin (desipramine hydrochloride) is to be combined with other psychotropic agents such as tranquilizers or sedative/hypnotics, careful consideration should be given to the pharmacology of the agents employed since the sedative effects of Norpramin and benzodiazepines (e.g., chlordiazepoxide or diazepam) are additive. Both the sedative and anticholinergic effects of the major tranquilizers are also additive to those of Norpramin.
- Concurrent administration of cimetidine and tricyclic antidepressants can produce clinically significant increases in the plasma levels of the tricyclic antidepressants. Conversely, decreases in plasma levels of the tricyclic antidepressants have been reported upon discontinuation of cimetidine which may result in the loss of the therapeutic efficacy of the tricyclic antidepressant.
- This drug should be discontinued as soon as possible prior to elective surgery because of the possible cardiovascular effects. Hypertensive episodes have been observed during surgery in patients taking desipramine hydrochloride.
- Both elevation and lowering of blood sugar levels have been reported.
- Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is evidence of pathologic neutrophil depression.

### ADVERSE REACTIONS

Note: Included in the following listing are a few adverse reactions that have not been reported with this specific drug. However, the pharmacologic similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when Norpramin (desipramine hydrochloride) is given.

**Cardiovascular:** hypotension, hypertension, tachycardia, palpitation, arrhythmias, heart block, myocardial infarction, stroke. There has been a report of an "acute collapse" and

"sudden death" in an eight-year old (18 kg) male, treated for two years for hyperactivity. (See WARNINGS, Use in Children.)

**Psychiatric:** confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness; agitation; insomnia and nightmares; hypomania; exacerbation of psychosis.

**Neurologic:** numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures; alteration in EEG patterns; tinnitus.

**Anticholinergic:** dry mouth, and rarely associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis, increased intraocular pressure; constipation, paralytic ileus; urinary retention, delayed micturition, dilatation of urinary tract.

**Allergic:** skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight), edema (of face and tongue or general), drug fever, cross sensitivity with other tricyclic drugs.

**Hematologic:** bone marrow depressions including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

**Gastrointestinal:** anorexia, nausea and vomiting, epigastric distress, peculiar taste, abdominal cramps, diarrhea, stomatitis, black tongue.

**Endocrine:** gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence, painful ejaculation, testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate antidiuretic hormone secretion (SIADH).

**Other:** jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration, flushing; urinary frequency, nocturia; parotid swelling; drowsiness, dizziness, weakness and fatigue, headache, alopecia.

**Withdrawal Symptoms:** Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

### OVERDOSAGE

There is no specific antidote for desipramine, nor are there specific phenomena of diagnostic value characterizing poisoning by the drug.

Within an hour of ingestion the patient may become agitated or stuporous and then comatose. Hypotension, shock, and renal shutdown may ensue. Grand mal seizures, both early and late after ingestion, have been reported. Hyperactive reflexes, hyperpyrexia, muscle rigidity, vomiting, and ECG evidence of impaired conduction may occur. Serious disturbances of cardiac rate, rhythm, and output can occur. The precepts of early evacuation of the ingested material and subsequent support of respiration (airway and movement), circulation, and renal output apply.

The principles of management of coma and shock by means of the mechanical respirator, cardiac pacemaker, monitoring of central venous pressure, and regulation of fluid and acid-base balance are well known in most medical centers and are not further discussed here. Because CNS involvement, respiratory depression, and cardiac arrhythmia can occur suddenly, hospitalization and close observation are generally advisable, even when the amount ingested is thought to be small or the initial degree of intoxication appears slight or moderate. Most patients with ECG abnormalities should have continuous cardiac monitoring for at least 72 hours and be closely observed until well after cardiac status has returned to normal; relapses may occur after apparent recovery.

The slow intravenous administration of physostigmine salicylate has been reported to reverse most of the anticholinergic cardiovascular and CNS effects of overdose with tricyclic antidepressants. In adults, 1 to 3 mg has been reported to be effective. In children, the dose should be started with 0.5 mg and repeated at 5-minute intervals to determine the minimum effective dose; no more than 2 mg should be given. Because of the short duration of action of physostigmine, the effective dose should be repeated at 30-minute to 60-minute intervals, as necessary. Rapid injection should be avoided to reduce the possibility of physostigmine-induced convulsions.

Other possible therapeutic considerations include:

- Dialysis: Desipramine is found in low concentration in the serum, even after a massive oral dose. In vitro experiments in which blood bank blood was used indicate that it is very poorly dialyzed. Because of indications that the drug is secreted in gastric juice, constant gastric lavage has been suggested.
- Pharmacologic treatment of shock: Since desipramine potentiates the action of such vasopressor agents as levaterenol and metaraminol, they should be used only with caution.
- Pharmacologic control of seizures: Intravenous barbiturates are the treatment of choice for the control of grand mal seizures. One may, alternatively, consider the parenteral use of diphenylhydantoin, which has less central depressant effect but also has an effect on heart rhythm that has not yet been fully defined.
- Pharmacologic control of cardiac function: Severe disturbances of cardiac rate, rhythm, and output are probably the initiating events in shock. Intravenous volume must be maintained by i.v. fluids. Digitalization should be carried out early in view of the fact that a positive inotropic effect can be achieved without increase in cardiac work. Many of the cardiodynamic effects of digitalis are the exact opposite of those of massive doses of desipramine (animal studies).

Product Information as of January, 1989

Y398D

MERRELL DOW PHARMACEUTICALS INC.  
Cincinnati, Ohio 45215, U.S.A.

**Merrell Dow**



# Introducing **HALDOL® Decanoate 100** (HALOPERIDOL) INJECTION

**Less volume per injection  
can enhance patient acceptance**

New 100 mg/mL formulation is twice the concentration  
of the original 50 mg/mL decanoate formulation

- For many patients, fewer injections per dose may reduce anxiety and enhance patient compliance
- Multi-dose vial packaging means convenience for you and your staff



Please see brief summary of Prescribing Information on next page.

During dose adjustment or episodes of exacerbation of psychotic symptoms, therapy with HALDOL Decanoate 100 or HALDOL Decanoate 50 can be supplemented with short-acting forms of HALDOL® (haloperidol). The side effects of the decanoate products are those of HALDOL. The prolonged action of HALDOL Decanoate 100 and HALDOL Decanoate 50 should be considered in the management of side effects.

 **McNEIL  
PHARMACEUTICAL**  
McNEILAB, INC. Spring House, PA 19477

**HALDOL® Decanoate 100**  
(HALOPERIDOL) INJECTION 100mg/mL  
**HALDOL® Decanoate 50**  
(HALOPERIDOL) INJECTION 50mg/mL



# HALDOL® Decanoate 100

(HALOPERIDOL) INJECTION 100mg/mL

# HALDOL® Decanoate 50

(HALOPERIDOL) INJECTION 50mg/mL

For IM Injection Only

The following is a brief summary only. Before prescribing, see complete prescribing information in HALDOL and HALDOL Decanoate product labeling.

**Contraindications:** Since the pharmacologic and clinical actions of HALDOL Decanoate 50 and HALDOL Decanoate 100 are attributed to HALDOL haloperidol as the active medication, Contraindications, Warnings, and additional information are those of HALDOL, modified to reflect the prolonged action.

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

**Warnings:** *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

*Neuroleptic Malignant Syndrome (NMS):* A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with HALDOL.

*Usage in Pregnancy:* (see PRECAUTIONS—Usage in Pregnancy) *Combined Use With Lithium:* (see PRECAUTIONS—Drug Interactions)

*General:* Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS—Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

**Precautions:** Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinson medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intracranial pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL.

The 1, 5, 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

*Information for Patients:* Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

*Drug Interactions:* Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear. As with other antipsychotic agents, it should be noted that HALDOL may be capable of potentiating CNS depressants such as anesthetics, opiates, and alcohol.

*Carcinogenesis, Mutagenesis and Impairment of Fertility:* No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsomal activation assay.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecostasia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

*Usage in Pregnancy:* Pregnancy Category C. Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards to the fetus.

*Nursing Mothers:* Infants should not be nursed during drug treatment.

*Pediatric Use:* Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

**Adverse Reactions:** Adverse reactions following the administration of HALDOL Decanoate 50 or HALDOL Decanoate 100 are those of HALDOL haloperidol. Since vast experience has accumulated with HALDOL, the adverse reactions are reported for that compound as well as for haloperidol decanoate. As with all injectable medications, local tissue reactions have been reported with haloperidol decanoate.

*CNS Effects: Extrapyramidal Reactions—*Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which when first observed were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases. *Withdrawal Emergent Neurological Signs—*Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available HALDOL should be gradually withdrawn. *Tardive Dyskinesia—*As with all antipsychotic agents HALDOL has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients irreversible. The syndrome is characterized by rhythmic involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk. There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked. It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop. *Tardive Dystonia—*Tardive dystonia, not associated with the above syndrome, has also been reported. Tardive dystonia is characterized by delayed onset of choreic or dystonic movements, is often persistent, and has the potential of becoming irreversible. *Other CNS Effects—*Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

*Body as a Whole:* Neuroleptic malignant syndrome (NMS), hyperpyrexia and heat stroke have been reported with HALDOL. (See WARNINGS for further information concerning NMS.) *Cardiovascular Effects:* Tachycardia, hypotension, hypertension and ECG changes. *Hematologic Effects:* Reports of mild, usually transient, leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication. *Liver Effects:* Impaired liver function and/or jaundice. *Dermatologic Reactions:* Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. *Endocrine Disorders:* Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecostasia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia. *Gastrointestinal Effects:* Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. *Autonomic Reactions:* Dry mouth, blurred vision, urinary retention, diaphoresis, and priapism. *Respiratory Effects:* Laryngospasm, bronchospasm and increased depth of respiration. *Special Senses:* Cataracts, retinopathy and visual disturbances. *Other:* Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

**IMPORTANT:** Full directions for use should be read before HALDOL or HALDOL Decanoate products are administered or prescribed. For information on symptoms and treatment of overdosage, see full prescribing information.

The short-acting HALDOL injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

McNeil Pharmaceutical, McNEILAB, INC., Spring House, PA 19477

8/23/89



You are invited to  
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# Clinical Approaches to the Treatment of Depression in the 1990s

**CHAIRMAN**

**Samuel Gershon, MD**  
Western Psychiatric Institute and Clinic

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Western Psychiatric Institute and Clinic

**"Addiction and Depression"**

**Jonathan Himmelhoch, MD**  
Western Psychiatric Institute and Clinic

**"Depression Case Profiles:  
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and Dismal Failures"**

**James Jefferson, MD**  
University of Wisconsin Medical School

**"Treatment of the  
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**Gary Tollefson, MD, PhD**  
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**American Psychiatric  
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**Sunday, May 13, 1990  
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Refreshments**

**Sheraton Centre  
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CME Credit: The American Psychiatric Association designates this continuing medical education activity for 3 credit hours in Category I of the Physician's Recognition Award of the American Medical Association and for the CME requirements of the APA.

**Sponsored by an educational grant  
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# Calendar

*For free listing of your organization's official annual or regional meeting, please send us the following information: sponsor, location, inclusive dates, type and number of continuing education credits (if available), and the name, address, and telephone number of the person or group to contact for more information. All notices and changes must be received no later than 120 days before the first day of the month of desired publication and should be addressed to Calendar, American Journal of Psychiatry, 1400 K St., N.W., Washington, DC 20005. Because of space limitations, only listings of meetings of the greatest interest to Journal readers will be included.*

## JUNE

June 3–6, annual meeting, Canadian College of Neuropsychopharmacology, Banff, Alberta. Contact Glen Baker, Chairman, Organizing Committee, Neurochemical Research Unit, Department of Psychiatry, Mackenzie Centre, University of Alberta, Edmonton, Alberta, Canada, T6G 2B7; 403-492-6591.

June 5–6, international conference, "Autoimmunity—new targets and therapeutic approaches," Royal College of Physicians, London. Contact Renata Duke, IBC Technical Services Ltd., Bath House (3rd Floor), 56 Holborn Viaduct, London, EC1A 2EX, United Kingdom; 01-236-4080.

June 6–8, 5th Congress of the International Federation of Psychiatric Epidemiology, Montreal. Contact Head Office of the Congress, 2 Complexe Desjardins (East Tower), Entrance 3000, P.O. Box 216, Station Desjardins, Montreal, Quebec, Canada, H5B 1C8; 514-845-3259.

June 11–12, 4th Annual National Institute of Mental Health International Research Conference on the Classification and Treatment of Mental Disorders in General Health Care Settings, Rockville, Md. Contact David B. Larson, M.D., M.S.P.H., or Kelly H. Kelleher, M.D., M.P.H., c/o The Primary Care Research Program, Biometric and Clinical Applications Branch, Division of Biometry and Applied Sciences, National Institute of Mental Health, 5600 Fishers Lane, Room 18C-14, Rockville, MD 20857; 301-443-1330.

June 13–15, 1st International Conference on "Crisis Intervention Approach in Mental Health," Regents College, London. Contact Dr. N. Rao Punukollu, Coordinator, International Scientific Advisory Group, 63 Nabcroft Lane, Crosland Moor, Huddersfield, HD4 5DU, W. Yorkshire, England; 0484-654711, ext. 3588.

June 13–15, annual meeting, Association of Directors of Medical Student Education in Psychiatry, Tucson. Contact John Racy, M.D., President, 1501 North Campbell Avenue, Tucson, AZ 85724; 602-626-6512.

June 13–15, 100th Anniversary, Department of Psychiatry, University of Liege, "Biological Markers of Depression: State of the Art," Liege. Contact M. Ansseau or R. von Frenckell, Psychiatric Unit, C.H.U. du Sart Tilman (B35), B-4000 Liege, Belgium; (32) 41307960.

June 14–17, annual meeting, American Association of Neuropathologists, San Francisco. Contact Reid R. Heffner, Jr., M.D., Secretary-Treasurer, 462 Grider Street, Buffalo, NY 14215; 716-898-3117.

June 15–20, annual meeting, American Nurses' Association, Boston. Contact Barbara Rećman, R.N., Executive Director, 2420 Pershing Road, Kansas City, MO 64108; 816-474-5720.

June 16–19, "Neurological and Neuropsychological Complications of HIV Infection: Update 1990," a conference prior to the VI International Conference on AIDS, Monterey, California. Contact Conference Secretariat, Kenness Canada, Inc., P.O. Box 200, Station B, Montreal, Quebec, Canada H3B 3J7; 514-874-1622.

June 18–20, International Conference on Social Stress Research, London. Contact Kimberly Vogt, Conference Coordinator, Dean's Office, College of Liberal Arts, Murkland Hall, University of New Hampshire, Durham, New Hampshire 03824.

June 20–24, 6th International Conference on AIDS, San Francisco. Contact Robert M. Wachter, M.D., Program Director, Suite 300, 655 Fifteenth Street, NW, Washington, DC 20005; 202-639-5179.

June 24–27, 3rd Symposium on Violence and Aggression, Saskatoon, Saskatchewan. Contact Thelma Howard, Planning Committee, Division of Extension and Community Relations, University of Saskatchewan, Saskatoon, Saskatchewan, Canada S7N 0W0.

June 24–28, annual meeting, American Medical Association, Chicago. Contact James H. Sammons, M.D., Executive Vice-President, 535 N. Dearborn Street, Chicago, IL 60610; 312-645-5000.

June 24–28, 6th Annual Conference on Children-in-War, Jerusalem. Contact Dr. Roberta Apfel, Program Director, Sigmund Freud Center, Hebrew University of Jerusalem, Mount Scopus, Jerusalem 91905 Israel; 02-883-380.

June 24–29, annual meeting, International Council on Social Welfare, Marrakech, Morocco. Contact Ingrid Gelinek, Koestergasse 1/29, A-1060 Vienna, Austria; 0222/587 81 64.

(Continued on page A68)



**PAMELOR®** (nortriptyline HCl)**BRIEF SUMMARY.**

Please see package insert for full prescribing information.

**Contraindications:** 1) Concurrent use with a monoamine oxidase (MAO) inhibitor, since hyperpyretic crises, severe convulsions, and fatalities have occurred when similar tricyclic antidepressants were used in such combinations; MAO inhibitors should be discontinued for at least two weeks before treatment with Pamelor® (nortriptyline HCl) is started. 2) Hypersensitivity to Pamelor® (nortriptyline HCl), cross-sensitivity with other dibenzazepines is a possibility. 3) The acute recovery period after myocardial infarction.

**Warnings:** Give only under close supervision to patients with cardiovascular disease, because of the tendency of the drug to produce sinus tachycardia and to prolong conduction time; myocardial infarction, arrhythmia, and strokes have occurred. The antihypertensive action of guanethidine and similar agents may be blocked. Because of its anticholinergic activity, nortriptyline should be used with great caution in patients who have glaucoma or a history of urinary retention. Patients with a history of seizures should be followed closely, since nortriptyline is known to lower the convulsive threshold. Great care is required in hyperthyroid patients or those receiving thyroid medication, since cardiac arrhythmias may develop. Nortriptyline may impair the mental and/or physical abilities required for the performance of hazardous tasks, such as operating machinery or driving a car; therefore, the patient should be warned accordingly. Excessive consumption of alcohol may have a potentiating effect, which may lead to the danger of increased suicidal attempts or overdose, especially in patients with histories of emotional disturbances or suicidal ideation.

The concomitant administration of quinidine and nortriptyline may result in a significantly longer plasma half-life, higher A.U.C. and lower clearance of nortriptyline.

**Use in Pregnancy:**—Safe use during pregnancy and lactation has not been established; therefore, in pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards.

**Use in Children:**—Not recommended for use in children, since safety and effectiveness in the pediatric age group have not been established.

**Precautions:** Use in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms; in overactive or agitated patients, increased anxiety and agitation may occur; in manic-depressive patients, symptoms of the manic phase may emerge. Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed patients. Troublesome patient hostility may be aroused. Epileptiform seizures may accompany administration. Close supervision and careful adjustment of dosage are required when used with other anticholinergic drugs and sympathomimetic drugs. Concurrent administration of cimetidine can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressant. Patients should be informed that the response to alcohol may be exaggerated. When essential, may be administered with electroconvulsive therapy, although the hazards may be increased. Discontinue the drug for several days, if possible, prior to elective surgery. The possibility of a suicidal attempt by a depressed patient remains after the initiation of treatment; in this regard, it is important that the least possible quantity of drug be dispensed at any given time. Both elevation and lowering of blood sugar levels have been reported. A case of significant hypoglycemia has been reported in a type II diabetic patient maintained on chlorpropamide (250 mg/day), after the addition of nortriptyline (125 mg/day).

**Adverse Reactions:** *Cardiovascular*—Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke. *Psychiatric*—Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia, panic, nightmares; hypomania; exacerbation of psychosis. *Neurologic*—Numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures; alteration in EEG patterns; tinnitus. *Anticholinergic*—Dry mouth and, rarely, associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract. *Allergic*—Skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); edema (general or of face and tongue); drug fever, cross-sensitivity with other tricyclic drugs. *Hematologic*—Bone marrow depression, including agranulocytosis; eosinophilia; purpura, thrombocytopenia. *Gastrointestinal*—Nausea and vomiting, anorexia, epigastric distress, diarrhea, peculiar taste, stomatitis, abdominal cramps, black-tongue. *Endocrine*—Gynecomastia in the male, breast enlargement and galactorrhea in the female, increased or decreased libido, impotence; testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate ADH (antidiuretic hormone) secretion. *Other*—Jaundice (simulating obstructive); altered liver function; weight gain or loss; perspiration; flushing; urinary frequency, nocturia; drowsiness, dizziness, weakness, fatigue, headache; parotid swelling; alopecia. *Withdrawal Symptoms*—Though these are not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

**Overdose:** Toxic overdose may result in confusion, restlessness, agitation, vomiting, hyperpyrexia, muscle rigidity, hyperactive reflexes, tachycardia. ECG evidence of impaired conduction, shock, congestive heart failure, stupor, coma, and CNS stimulation with convulsions followed by respiratory depression. Deaths have occurred with drugs of this class. No specific antidote is known; general supportive measures are indicated, with gastric lavage.

[PAM-219—9/1/89]

**SANDOZ PHARMACEUTICALS**  
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# Productive Days... Restful Nights and Pamelor® (nortriptyline HCl)



The Full-Time Antidepressant  
for patients whose symptoms include  
insomnia and anxiety

  
**PAMELOR®**  
(nortriptyline HCl)

CAPSULES: 10 mg, 25 mg, 50 mg, and 75 mg; SOLUTION: 10 mg/5 mL and alcohol 4%

*The active metabolite of amitriptyline*



## **Anxiety: THE *BURDEN* OF ILLNESS**

Panic disorder.  
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Obsessive-compulsive  
disorder. Depression.  
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illnesses is often  
complicated by the  
coexistence of clinical  
anxiety.

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the 143rd Annual  
Meeting of the American  
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**MAY 13-16, 1990**

Breakfast begins at 6:15 a.m.  
Symposia begin at 7:15 a.m.

Grand Ballroom  
Third Floor  
New York Hilton  
New York, New York

### **CHAIRPERSON**

**Robert O. Pasnau, MD**  
Professor and Director  
Adult Psychiatry  
Clinical Services  
UCLA School of Medicine  
Past President, American  
Psychiatric Association

**SUNDAY, MAY 13, 1990**

### **Anxiety and Panic Disorder**

#### **Opening Comments**

**Herbert Pardes, M.D.**  
President, American  
Psychiatric Association  
Vice President for  
Health Sciences  
Professor and Chairman,  
Department of Psychiatry  
College of Physicians  
and Surgeons  
Columbia University  
New York, New York

#### **The Hidden Patient**

**Myrna M. Weissman, Ph.D.**  
Professor of Epidemiology  
in Psychiatry, College of  
Physicians and Surgeons  
Columbia University  
New York, New York

#### **Managing Long-term Therapy**

**Graham D. Burrows, A.O., M.D.**  
Director, Division of  
Psychological Medicine  
Professor of Psychiatry  
University of Melbourne  
Austin Hospital  
Heidelberg, Victoria, Australia

**MONDAY, MAY 14, 1990**

### **Anxiety and Adjustment Disorder**

#### **Opening Comments**

**Elissa P. Benedek, M.D.**  
President Elect, American  
Psychiatric Association  
Director of Training  
and Research  
Center for Forensic Psychiatry  
Clinical Professor of Psychiatry  
University of Michigan  
Ann Arbor, Michigan

### **Psychosocial Stressors**

**Richard H. Rahe, M.D.**  
Past President, American  
Psychosomatic Society  
Professor of Psychiatry and  
Biobehavioral Sciences  
University of Nevada  
School of Medicine  
Reno, Nevada

#### **A Treatment Approach**

**Alan F. Schatzberg, M.D.**  
Associate Professor  
of Psychiatry  
Harvard Medical School  
Clinical Director  
Massachusetts Mental  
Health Center  
Boston, Massachusetts

**TUESDAY, MAY 15, 1990**

### **Anxiety and Obsessive- Compulsive Disorder**

#### **Opening Comments**

**Daniel X. Freedman, M.D.**  
Past President  
American Psychiatric  
Association  
Judson Braun Professor of  
Psychiatry and Pharmacology  
Acting Director  
Neuropsychiatric Institute  
UCLA School of Medicine  
Los Angeles, California

#### **The Waking Nightmare**

**Judith L. Rapoport, M.D.**  
Chief, Child Psychiatry  
Branch, National Institute of  
Mental Health  
Author, *The Boy Who  
Couldn't Stop Washing*  
Bethesda, Maryland

#### **Treating the Anxiety**

**John H. Greist, M.D.**  
Professor of Psychiatry  
Director, Obsessive-  
Compulsive Information  
Center, Co-Director, Anxiety  
Disorders Center  
University of Wisconsin  
Madison, Wisconsin

**WEDNESDAY, MAY 16, 1990**

### **Anxiety and Depression**

#### **Opening Comments**

**Paul Jay Fink, M.D.**  
Past President, American  
Psychiatric Association  
Chairman, Department  
of Psychiatry  
Albert Einstein  
Medical Center  
Philadelphia, Pennsylvania

#### **The Co-Morbidity Factor**

**Paula J. Clayton, M.D.**  
Professor and Head  
Department of Psychiatry  
University of Minnesota  
Minneapolis, Minnesota

#### **Targeting Treatment**

**Jan Fawcett, M.D.**  
Professor and Chairman  
Department of Psychiatry  
Rush-Presbyterian-St. Luke's  
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Chicago, Illinois

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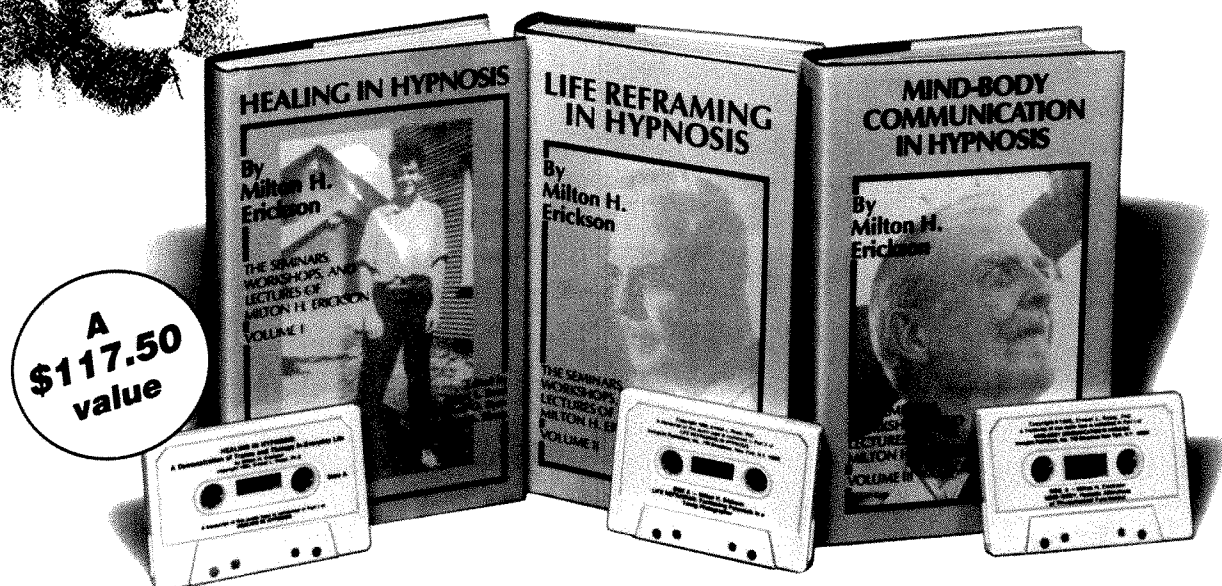


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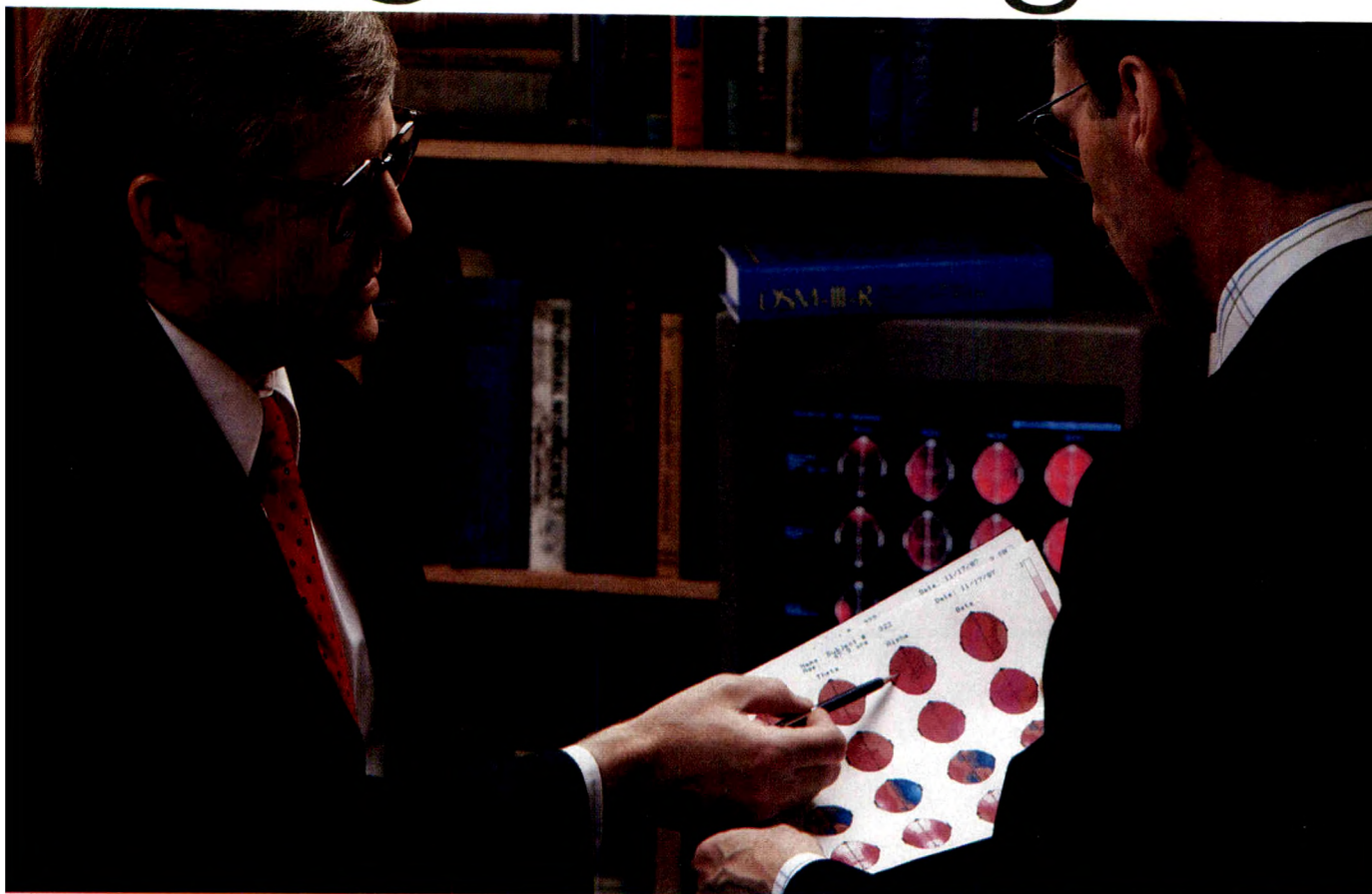
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HOW AVAILABLE FOR DEPRESSION IN A WIDE RANGE OF PATIENTS

Feeling better  
Living better

**NEW Wellbutrin<sup>®</sup>**

(BUPROPION HCl)

helps clear  
depression with  
few life-style  
disruptions.

See brief summary of full prescribing information  
on last pages of this advertisement.

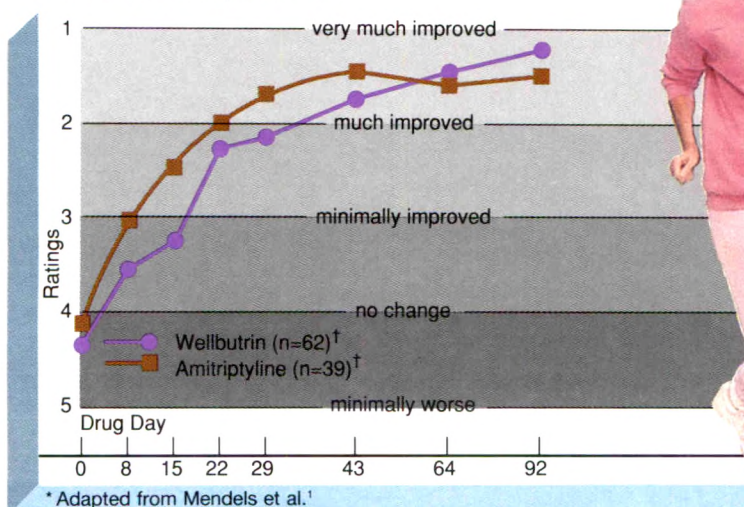


Chemically unique WELLBUTRIN

# Helps clear depression with few life-style disruptions.

## Relieves depression as effectively as amitriptyline.

Clinical Global Improvement\*

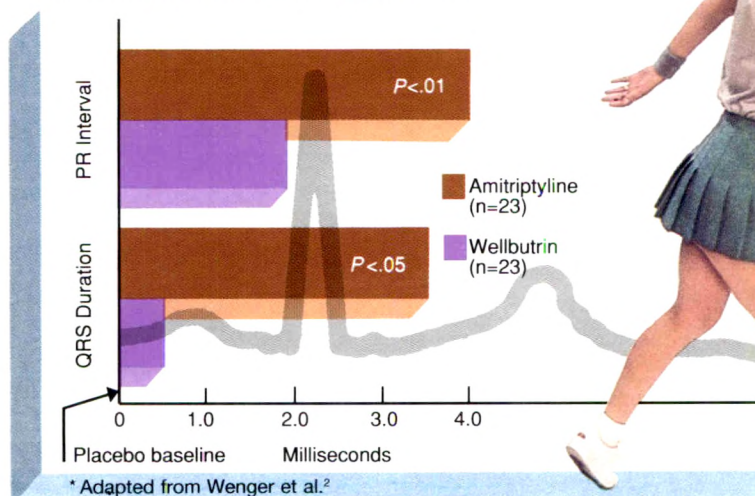


<sup>†</sup>Dosages were 300 to 450 mg/day for WELLBUTRIN, 75 to 150 mg/day for amitriptyline.

Please review IMPORTANT CONSIDERATIONS BEFORE PRESCRIBING WELLBUTRIN and brief summary on the last pages of this advertisement before prescribing WELLBUTRIN.

## Relieves depression with no clinically significant effect on cardiac conduction.

Average Change in EKG Parameters from Baseline Values During Treatment\*



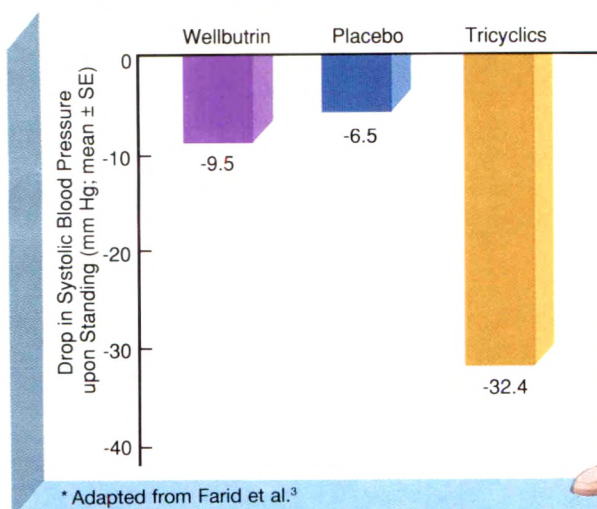
"By contrast, the present results with bupropion support the in vitro data demonstrating that this antidepressant lacks these undesirable electrophysiologic properties, and imply that bupropion has a substantially wider margin of safety in man than amitriptyline with regard to cardiac conduction."<sup>2</sup>



Feeling better  
Living better

**Relieves depression with  
no clinically significant  
orthostatic hypotension.**

Orthostatic Blood Pressure Change (mm Hg)\*



**NEW** **Wellbutrin<sup>®</sup>**  
(BUPROPION HCl)

**Helps clear depression with few life-style disruptions.**

See brief summary of full prescribing information  
on last pages of this advertisement.

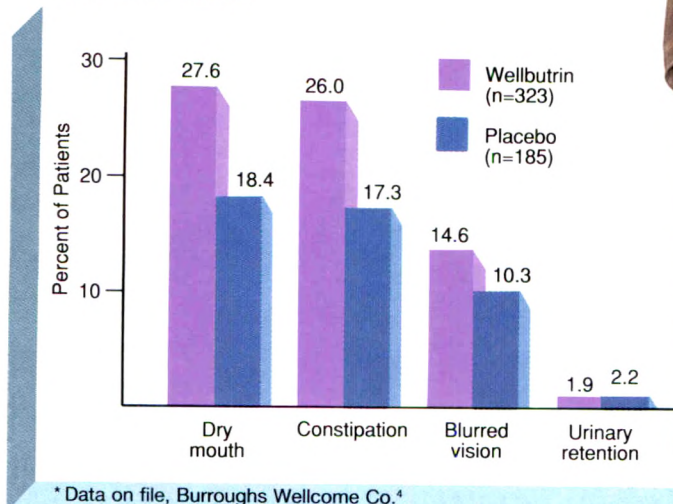


Chemically unique WELLBUTRIN

# Helps clear depression with few life-style disruptions.

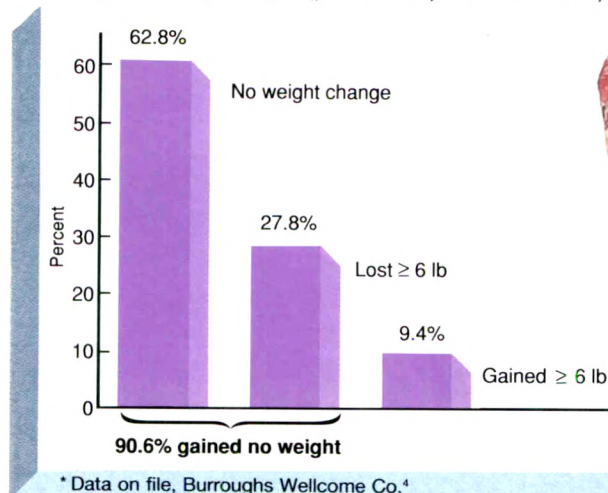
## Relieves depression with few anticholinergic side effects.

Percent Difference in Anticholinergic Effects  
Relative to Placebo\*



## Relieves depression with little or no weight gain.

Change in Body Weight (percent of patients; n=341)\*

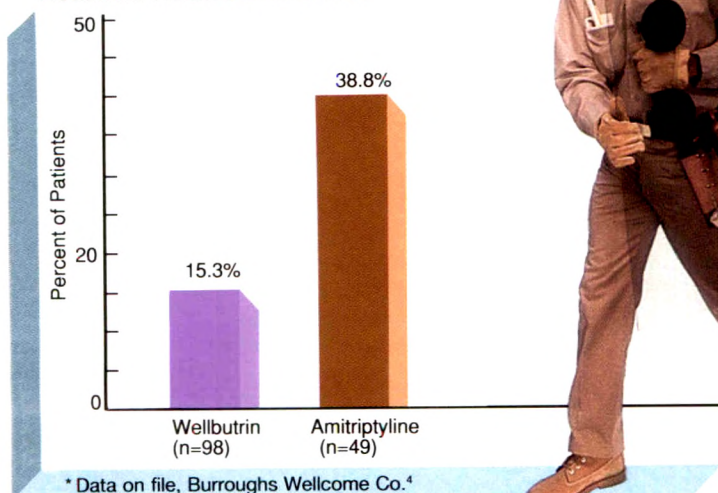




Feeling better  
Living better

**Relieves depression with little or no daytime drowsiness.**

Percent of Patients Reporting Treatment-Related Drowsiness\*



In placebo-controlled clinical trials, the incidence of drowsiness\* for patients treated with WELLBUTRIN was 19.8%, versus 19.5% for those receiving placebo.

**Agitation and Insomnia:** A substantial proportion of patients treated with WELLBUTRIN experience some degree of increased restlessness, agitation, anxiety, and insomnia, especially shortly after initiation of treatment. In clinical studies, these symptoms were sometimes of sufficient magnitude to require treatment with sedative/hypnotic drugs. In approximately 2% of patients, symptoms were sufficiently severe to require discontinuation of WELLBUTRIN treatment.

\*As with all drugs in this category, patients should be cautioned that the ability to perform tasks requiring judgment or motor and cognitive skills may be impaired.

**NEW**

**Wellbutrin<sup>®</sup>**  
(BUPROPION HCl)

**Helps clear depression with few life-style disruptions.**

See brief summary of full prescribing information on last pages of this advertisement.



Feeling better  
Living better

## Wellbutrin helps clear depression with few life-style disruptions.

### Important considerations before prescribing WELLBUTRIN.

#### Patient Selection Criteria

WELLBUTRIN is contraindicated in patients

- with a seizure disorder
- with a current or prior diagnosis of bulimia or anorexia nervosa
- on monoamine oxidase (MAO) inhibitor therapy
- who are allergic to it

(See CONTRAINDICATIONS section of full prescribing information.)

WELLBUTRIN should be administered with extreme caution to patients

- with a history of seizure, cranial trauma, or other factors that predispose toward seizure
- taking other agents or other treatment regimens that may lower seizure threshold

(See WARNINGS section of full prescribing information.)

#### Overdosage

In 13 cases of overdose involving WELLBUTRIN, there were no deaths or lasting sequelae.

#### Seizures

A wide range of seizure rates has been reported with antidepressant therapy with some reports as low as 0.1%. The incidence of seizures with WELLBUTRIN is approximately 0.4%, which may be as much as fourfold higher than some other antidepressants, although no direct comparative studies have been conducted.

#### Dosage and Administration

The recommended starting dose of WELLBUTRIN is 200 mg/day given as 100 mg b.i.d. Based on clinical response, this dose may be increased to 300 mg/day given as 100 mg t.i.d. no sooner than three days after beginning therapy.

#### Dosing Regimen

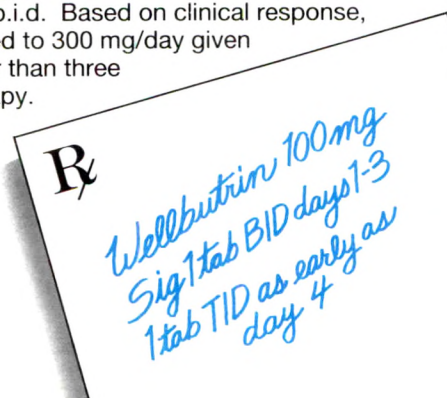
Treatment Day	Total Daily Dose	Tablet Strength	Number of Tablets		
			Morning	Midday	Evening
1-3	200 mg	100 mg	1	0	1
4	300 mg	100 mg	1	1	1

An increase in dosage, up to a maximum of 450 mg/day, given in divided doses of not more than 150 mg each, may be considered for patients in whom no clinical improvement is noted after several weeks of treatment at 300 mg/day. Increases in dose should not exceed 100 mg/day in a three-day period. WELLBUTRIN is available in both 75 mg and 100 mg tablets.

**Important: No single dose of WELLBUTRIN should exceed 150 mg because a higher incidence of seizures has been observed in patients receiving higher individual doses of WELLBUTRIN. For this reason, too, patients should be reminded that they should not double up on any dose because they missed a previous one. Dosage should not exceed 450 mg per day (see WARNINGS).**

Clinical trials involving more than 7,000 depressed patients and over 200 investigators demonstrated that **WELLBUTRIN relieves depression in a wide range of patients:**

- with no clinically significant effects on cardiac conduction
- with no clinically significant orthostatic hypotension
- with few anticholinergic side effects
- with little or no weight gain
- with little or no daytime drowsiness



**NEW**  
**Wellbutrin**<sup>®</sup>  
(BUPROPION HCl)

See brief summary of full prescribing information on last pages of this advertisement.



## WELLBUTRIN® (BUPROPION HYDROCHLORIDE) Tablets

Before prescribing, please consult complete product information, a summary of which follows:

**INDICATIONS AND USAGE:** Wellbutrin is indicated for the treatment of depression. A physician considering the initiation of Wellbutrin should be aware that the drug may cause generalized seizures with an approximate incidence of 0.4% (4/1000). This incidence may exceed that of other antidepressants as much as fourfold. This relative risk is only an approximation since no direct comparative studies have been conducted.

**CONTRAINDICATIONS:** Wellbutrin is contraindicated in patients: with a seizure disorder; with a current or prior diagnosis of bulimia or anorexia nervosa, because of a higher incidence of seizures noted in such patients; who have shown an allergic response to it; or who are currently being treated with an MAO inhibitor. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with Wellbutrin.

### WARNINGS:

**SEIZURES:** Wellbutrin is associated with seizures in approximately 0.4% (4/1000) of patients treated at doses up to 450 mg/day. This incidence of seizures may exceed that of other marketed antidepressants by as much as fourfold. This relative risk is only an approximate estimate because no direct comparative studies have been conducted. The estimated seizure incidence for Wellbutrin increases almost tenfold between 450 and 600 mg/day, which is twice the usually required daily dose (300 mg) and one and one-third the maximum recommended daily dose (450 mg). Given the wide variability among individuals and their capacity to metabolize and eliminate drugs, this disproportionate increase in seizure incidence with dose incrementation calls for caution in dosing.

During the pre-approval evaluation period, 25 among approximately 2400 patients treated with Wellbutrin experienced seizures. At the time of seizure, 7 patients were receiving daily doses of 450 mg or below, for an incidence of 0.33% (3/1000) within the recommended dose range. Twelve (12) patients experienced seizures at 600 mg per day (2.3% incidence); 6 additional patients had seizures at daily doses between 600 and 900 mg (2.8% incidence).

A separate, prospective study was conducted to determine the incidence of seizure during an 8 week treatment exposure in approximately 3200 additional patients who received daily doses of up to 450 mg. Patients were permitted to continue treatment beyond 8 weeks if clinically indicated. Eight (8) seizures occurred during the initial 8 week treatment period and 5 seizures were reported in patients continuing treatment beyond 8 weeks, resulting in a total seizure incidence of 0.4%.

The risk of seizure appears to be strongly associated with dose and the presence of predisposing factors. A significant predisposing factor (e.g., history of head trauma or prior seizure, CNS tumor, concomitant medications that lower seizure threshold, etc.) was present in approximately one-half of the patients experiencing a seizure. Sudden and large increments in dose may contribute to increased risk. While many seizures occurred early in the course of treatment, some seizures did occur after several weeks at fixed dose.

**Recommendations for reducing the risk of seizure:** Retrospective analysis of clinical experience gained during the development of Wellbutrin suggests that the risk of seizure may be minimized if (1) the total daily dose of Wellbutrin does not exceed 450 mg, (2) the daily dose is administered i.i.d., with each single dose not to exceed 150 mg to avoid high peak concentrations of bupropion and/or its metabolites, and (3) the rate of incrementation of dose is very gradual. Extreme caution should be used when Wellbutrin is (1) administered to patients with a history of seizure, cranial trauma, or other predisposition(s) toward seizure, or (2) prescribed with other agents (e.g., antipsychotics, other antidepressants, etc.) or treatment regimens (e.g., abrupt discontinuation of a benzodiazepine) that lower seizure threshold.

**Potential for Hepatotoxicity:** In rats receiving large doses of bupropion chronically, there was an increase in incidence of hepatic hyperplastic nodules and hepatocellular hypertrophy. In dogs receiving large doses of bupropion chronically, various histologic changes were seen in the liver, and laboratory tests suggesting mild hepatocellular injury were noted. Although scattered abnormalities in liver function tests were detected in patients participating in clinical trials, there is no clinical evidence that bupropion acts as a hepatotoxin in humans.

### PRECAUTIONS:

#### General:

**Agitation and Insomnia:** A substantial proportion of patients treated with Wellbutrin experience some degree of increased restlessness, agitation, anxiety, and insomnia, especially shortly after initiation of treatment. In clinical studies, these symptoms were sometimes of sufficient magnitude to require treatment with sedative/hypnotic drugs. In approximately 2% of patients, symptoms were sufficiently severe to require discontinuation of Wellbutrin treatment.

**Psychosis, Confusion, and Other Neuropsychiatric Phenomena:** Patients treated with Wellbutrin have been reported to show a variety of neuropsychiatric signs and symptoms including delusions, hallucinations, psychotic episodes, confusion, and paranoia. Because of the uncontrolled nature of many studies, it is impossible to provide a precise estimate of the extent of risk imposed by treatment with Wellbutrin. In several cases, neuropsychiatric phenomena abated upon dose reduction and/or withdrawal of treatment.

**Activation of Psychosis and/or Mania:** Antidepressants can precipitate manic episodes in Bipolar Manic Depressive patients during the depressed phase of their illness and may activate latent psychosis in other susceptible patients. Wellbutrin is expected to pose similar risks.

**Altered Appetite and Weight:** A weight loss of greater than 5 pounds occurred in 28% of Wellbutrin patients. This incidence is approximately double that seen in comparable patients treated with tricyclics or placebo. Furthermore, while 34.5% of patients receiving tricyclic antidepressants gained weight, only 9.4% of patients treated with Wellbutrin did. Consequently, if weight loss is a major presenting sign of a patient's depressive illness, the anorectic and/or weight reducing potential of Wellbutrin should be considered.

**Suicide:** The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Accordingly, prescriptions for Wellbutrin should be written for the smallest number of tablets consistent with good patient management.

**Use in Patients with Systemic Illness:** There is no clinical experience establishing the safety of Wellbutrin in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, care should be exercised if it is used in these groups. Wellbutrin was well tolerated in patients who had previously developed orthostatic hypotension while receiving tricyclic antidepressants.

Because bupropion HCl and its metabolites are almost completely excreted through the kidney and metabolites are likely to undergo conjugation in the liver prior to urinary excretion, treatment of patients with renal or hepatic impairment should be initiated at reduced dosage as bupropion and its metabolites may accumulate in such patients beyond concentrations expected in patients without renal or hepatic impairment. The patient should be closely monitored for possible toxic effects of elevated blood and tissue levels of drug and metabolites.

#### Information for Patients:

Patients should be instructed to take Wellbutrin in equally divided doses three or four times a day to minimize the risk of seizure.

Patients should be told that any CNS-active drug like Wellbutrin may impair their ability to perform tasks requiring judgment or motor and cognitive skills. Consequently, until they are reasonably certain that Wellbutrin does not adversely affect their performance they should refrain from driving an automobile or operating complex, hazardous machinery.

Patients should be told that the use and cessation of use of alcohol may alter the seizure threshold, and, therefore, that the consumption of alcohol should be minimized, and, if possible, avoided completely.

Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

**Drug Interactions:** No systematic data have been collected on the consequences of the concomitant administration of Wellbutrin and other drugs.

However, animal data suggest that Wellbutrin may be an inducer of drug metabolizing enzymes. This may be of potential clinical importance because the blood levels of co-administered drugs may be altered.

Alternatively, because bupropion is extensively metabolized, the co-administration of other drugs may affect its clinical activity. In particular, care should be exercised when administering drugs known to affect hepatic drug metabolizing enzyme systems (e.g., carbamazepine, cimetidine, phenobarbital, phenytoin).

Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAO inhibitor phenelzine (see CONTRAINDICATIONS).

Limited clinical data suggest a higher incidence of adverse experiences in patients receiving concurrent administration of Wellbutrin and L-dopa. Administration of Wellbutrin to patients receiving L-dopa concurrently should be undertaken with caution, using small initial doses and small gradual dose increases.

Concurrent administration of Wellbutrin and agents which lower seizure threshold should be undertaken only with extreme caution (see WARNINGS). Low initial dosing and small gradual dose increases should be employed.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Lifetime carcinogenicity studies were performed in rats and mice at doses up to 300 and 150 mg/kg/day, respectively. In the rat study there was an increase in nodular proliferative lesions of the liver at doses of 100 to 300 mg/kg/day; lower doses were not tested. The question of whether or not such lesions may be precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in either study.

Bupropion produced a borderline positive response (2-3 times control mutation rate) in some strains in the Ames bacterial mutagenicity test, and a high oral dose (300, but not 100 or 200 mg/kg) produced a low incidence of chromosomal aberrations in rats. The relevance of these results in estimating the risk of human exposure to therapeutic doses is unknown.

A fertility study was performed in rats; no evidence of impairment of fertility was encountered at oral doses up to 300 mg/kg/day.

**Pregnancy: Teratogenic Effects:** Pregnancy Category B: Reproduction studies have been performed in rabbits and rats at doses up to 15-45 times the human daily dose and have revealed no definitive evidence of impaired fertility or harm to the fetus due to bupropion. (In rabbits, a slightly increased incidence of fetal abnormalities was seen in two studies, but there was no increase in any specific abnormality). There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

**Labor and Delivery:** The effect of Wellbutrin on labor and delivery in humans is unknown.

**Nursing Mothers:** Because of the potential for serious adverse reactions in nursing infants from Wellbutrin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric Use:** The safety and effectiveness of Wellbutrin in individuals under 18 years old have not been established.

**Use in the Elderly:** Wellbutrin has not been systematically evaluated in older patients.

**ADVERSE REACTIONS:** (See also WARNINGS and PRECAUTIONS) Adverse events commonly encountered in patients treated with Wellbutrin are agitation, dry mouth, insomnia, headache/migraine, nausea/vomiting, constipation, and tremor.

Adverse events were sufficiently troublesome to cause discontinuation of Wellbutrin treatment in approximately ten percent of the 2400 patients and volunteers who participated in the product's pre-approval clinical trials. The more common events causing discontinuation include neuropsychiatric disturbances (3.0%), primarily agitation and abnormalities in mental status; gastrointestinal disturbances (2.1%), primarily nausea and vomiting; neurological disturbances (1.7%), primarily seizures, headaches, and sleep disturbances; and dermatologic problems (1.4%), primarily rashes. It is important to note, however, that many of these events occurred at doses that exceed the recommended daily dose.



The table below is presented solely to indicate the relative frequency of adverse events reported in representative controlled clinical studies conducted to evaluate the safety and efficacy of Wellbutrin under relatively similar conditions of daily dosage (300-600 mg), setting, and duration (3-4 weeks). The figures cited cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors must differ from those which prevailed in the clinical trials. These incidence figures also cannot be compared with those obtained from other clinical studies involving related drug products as each group of drug trials is conducted under a different set of conditions.

Finally, it is important to emphasize that the tabulation does not reflect the relative severity and/or clinical importance of the events. A better perspective on the serious adverse events associated with the use of Wellbutrin is provided in the WARNINGS and PRECAUTIONS sections.

**TREATMENT EMERGENT ADVERSE EXPERIENCE INCIDENCE  
IN PLACEBO-CONTROLLED CLINICAL TRIALS\***  
(Percent of Patients Reporting)

Adverse Experience	Wellbutrin Patients (n = 323)	Placebo Patients (n = 185)	Adverse Experience	Wellbutrin Patients (n = 323)	Placebo Patients (n = 185)
<b>CARDIOVASCULAR</b>			<b>Dry Mouth</b>	27.6	18.4
Cardiac Arrhythmias	5.3	4.3	Excessive Sweating	22.3	14.6
Dizziness	22.3	16.2	Headache/Migraine	25.7	22.2
Hypertension	4.3	1.6	Impaired Sleep Quality	4.0	1.6
Hypotension	2.5	2.2	Increased Salivary Flow	3.4	3.8
Palpitations	3.7	2.2	Insomnia	18.6	15.7
Syncope	1.2	0.5	Muscle Spasms	1.9	3.2
Tachycardia	10.8	8.6	Pseudoparkinsonism	1.5	1.6
<b>DERMATOLOGIC</b>			Sedation	19.8	19.5
Pruritus	2.2	0.0	Sensory Disturbance	4.0	3.2
Rash	8.0	6.5	Tremor	21.1	7.6
<b>GASTROINTESTINAL</b>			<b>NEUROPSYCHIATRIC</b>		
Anorexia	18.3	18.4	Agitation	31.9	22.2
Appetite Increase	3.7	2.2	Anxiety	3.1	1.1
Constipation	26.0	17.3	Confusion	8.4	4.9
Diarrhea	6.8	8.6	Decreased Libido	3.1	1.6
Dyspepsia	3.1	2.2	Delusions	1.2	1.1
Nausea/Vomiting	22.9	18.9	Disturbed Concentration	3.1	3.8
Weight Gain	13.6	22.7	Euphoria	1.2	0.5
Weight Loss	23.2	23.2	Hostility	5.6	3.8
<b>GENITOURINARY</b>			<b>NONSPECIFIC</b>		
Impotence	3.4	3.1	Fatigue	5.0	8.6
Menstrual Complaints	4.7	1.1	Fever/Chills	1.2	0.5
Urinary Frequency	2.5	2.2	<b>RESPIRATORY</b>		
Urinary Retention	1.9	2.2	Upper Respiratory Complaints	5.0	11.4
<b>MUSCULOSKELETAL</b>			<b>SPECIAL SENSES</b>		
Arthritis	3.1	2.7	Auditory Disturbance	5.3	3.2
<b>NEUROLOGICAL</b>			Blurred Vision	14.6	10.3
Akathisia	1.5	1.1	Gustatory Disturbance	3.1	1.1
Akinesia/Bradykinesia	8.0	8.6			
Cutaneous Temperature Disturbance	1.9	1.6			

\*Events reported by at least 1% of Wellbutrin patients are included.

**Other events observed during the entire pre-approval evaluation of Wellbutrin:** During its pre-approval assessment, Wellbutrin was evaluated in almost 2400 subjects. The conditions and duration of exposure to Wellbutrin varied greatly and a substantial proportion of the experience was gained in open and uncontrolled clinical settings. During this experience, numerous adverse events were reported; however, without appropriate controls, it is impossible to determine with certainty which events were or were not caused by Wellbutrin. The following enumeration is organized by organ system and describes events in terms of their relative frequency of reporting in the data base. Events of major clinical importance are also described in the WARNINGS and PRECAUTIONS sections of the labeling.

The following definitions of frequency are used: Frequent adverse events are defined as those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to 1/1000 patients, while rare events are those occurring in less than 1/1000 patients.

**Cardiovascular:** Frequent was edema; infrequent were chest pain, EKG abnormalities (premature beats and nonspecific ST-T changes), and shortness of breath/dyspnea; and rare were pallor and phlebitis.

**Dermatologic:** Frequent were nonspecific rashes; infrequent were alopecia and dry skin; rare were change in hair color and hirsutism.

**Endocrine:** Infrequent was gynecomastia; rare were glycosuria and hormone level change.

**Gastrointestinal:** Infrequent were dysphagia, thirst disturbance, and liver damage/jaundice; rare were rectal complaints, colitis, G.I. bleeding, and intestinal perforation.

**Genitourinary:** Frequent was nocturia; infrequent were vaginal irritation, testicular swelling, urinary tract infection, painful erection, and retarded ejaculation; rare were dysuria, enuresis, urinary incontinence, menopause, ovarian disorder, pelvic infection, cystitis, dyspareunia, and painful ejaculation.

**Hematologic/Oncologic:** Rare was lymphadenopathy.

**Neurological:** (see WARNINGS) Frequent were ataxia/incoordination, seizure, myoclonus, dyskinesia, and dystonia; infrequent were mydriasis, vertigo, and dysarthria; and rare were EEG abnormality, abnormal neurological exam, impaired attention, and sciatica.

**Neuropsychiatric:** (see PRECAUTIONS) Frequent were mania/hypomania, increased libido, hallucinations, decrease in sexual function, and depression; infrequent were memory impairment, depersonalization, psychosis, dysphoria, mood instability, paranoia, formal thought disorder, and frigidity; rare was suicidal ideation.

**Oral Complaints:** Frequent was stomatitis; infrequent were toothache, bruxism, gum irritation, and oral edema; rare was glossitis.

**Respiratory:** Infrequent were bronchitis and shortness of breath/dyspnea; rare were epistaxis and rate or rhythm disorder.

**Special Senses:** Infrequent was visual disturbance; rare was diplopia.

**Nonspecific:** Frequent were flu-like symptoms; infrequent was nonspecific pain; rare were body odor, surgically related pain, infection, medication reaction and overdose.

**Post-Approval Reports:** The following additional events were rarely observed (less than 1/1000 patients) post-approval.

**Cardiovascular:** Flushing and myocardial infarction.

**Dermatologic:** Acne.

**Gastrointestinal:** Stomach ulcer.

**Hematologic/Oncologic:** Anemia and pancytopenia.

**Neurological:** Aphasia.

**Musculoskeletal:** Musculoskeletal chest pain.

**Respiratory:** Pneumonia and pulmonary embolism.

#### OVERDOSSAGE:

**Human overdose experience:** There has been limited clinical experience with overdosage of Wellbutrin. Thirteen overdoses occurred during clinical trials. Twelve patients ingested 850 to 4200 mg and recovered without significant sequelae. Another patient who ingested 9000 mg of Wellbutrin and 300 mg of tranylcypromine experienced a grand mal seizure and recovered without further sequelae.

#### DOSSAGE AND ADMINISTRATION:

**General Dosing Considerations:** It is particularly important to administer Wellbutrin in a manner most likely to minimize the risk of seizure (see WARNINGS). Increases in dose should not exceed 100 mg/day in a 3 day period. Gradual escalation in dosage is also important if agitation, motor restlessness, and insomnia, often seen during the initial days of treatment, are to be minimized. If necessary, these effects may be managed by temporary reduction of dose or the short-term administration of an intermediate to long-acting sedative hypnotic. A sedative hypnotic usually is not required beyond the first week of treatment. Insomnia may also be minimized by avoiding bedtime doses. If distressing, untoward effects supervene, dose escalation should be stopped.

No single dose of Wellbutrin should exceed 150 mg. Wellbutrin should be administered t.i.d., preferably with at least 6 hours between successive doses.

**Usual Dosage for Adults:** The usual adult dose is 300 mg/day, given t.i.d. Dosing should begin at 200 mg/day, given as 100 mg b.i.d. Based on clinical response, this dose may be increased to 300 mg/day, given as 100 mg t.i.d., no sooner than 3 days after beginning therapy (see table below).

Treatment Day	Total Daily Dose	Dosing Regimen Tablet Strength	Number of Tablets		
			Morning	Midday	Evening
1	200 mg	100 mg	1	0	1
4	300 mg	100 mg	1	1	1

**Increasing the Dosage Above 300 mg/Day:** As with other antidepressants, the full antidepressant effect of Wellbutrin may not be evident until 4 weeks of treatment or longer. An increase in dosage, up to a maximum of 450 mg/day, given in divided doses of not more than 150 mg each, may be considered for patients in whom no clinical improvement is noted after several weeks of treatment at 300 mg/day. Dosing above 300 mg/day may be accomplished using the 75 or 100 mg tablets. The 100 mg tablet must be administered q.i.d. with at least 4 hours between successive doses, in order not to exceed the limit of 150 mg in a single dose. Wellbutrin should be discontinued in patients who do not demonstrate an adequate response after an appropriate period of treatment at 450 mg/day.

**Elderly Patients:** In general, older patients are known to metabolize drugs more slowly and to be more sensitive to the anticholinergic, sedative, and cardiovascular side effects of antidepressant drugs.

#### References:

1. Mendels J, Amin MM, Chouinard G, et al. A comparative study of bupropion and amitriptyline in depressed outpatients. *J Clin Psychiatry*. 1983;44(5, sec 2):118-120.
2. Wenger TL, Cohn JB, Bustrack J. Comparison of the effects of bupropion and amitriptyline on cardiac conduction in depressed patients. *J Clin Psychiatry*. 1983;44(5, sec 2):174-175.
3. Farid FF, Wenger TL, Tsai SY, et al. Use of bupropion in patients who exhibit orthostatic hypotension on tricyclic antidepressants. *J Clin Psychiatry*. 1983;44(5, sec 2):170-173.
4. Data on file, Burroughs Wellcome Co.

# NEW Wellbutrin

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Harvard Medical School, and  
Chief, Clinical Psychopharmacology Unit  
Massachusetts General Hospital  
Boston, Massachusetts



### **Panic Disorder Across the Life Cycle: A Neurobiological Model**

**Dennis S. Charney, M.D.**  
Chief, Psychiatry Service  
West Haven VA Medical Center  
Associate Professor of Psychiatry  
Yale University School of Medicine  
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## Areas of discussion will include:

- The clinical picture of the problem schizophrenic
- The reintegrating schizophrenic patient
- Clozapine treatment: Long-term social outcome
- Tardive dyskinesia, clozapine and reintegration
- Psychosocial treatments and the reintegration of chronic schizophrenic patients

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CLO-390-01







(clozapine)  
TABLETS

**CAUTION:** Federal law prohibits dispensing without a prescription.

#### CONTRAINDICATIONS

CLOZARIL is contraindicated in patients with myeloproliferative disorders, or a history of CLOZARIL-induced agranulocytosis or severe granulocytopenia. CLOZARIL should not be used simultaneously with other agents having a well-known potential to suppress bone marrow function. As with more typical antipsychotic drugs, CLOZARIL is contraindicated in severe central nervous system depression or comatose states from any cause.

#### WARNINGS

##### General

BECAUSE OF THE SIGNIFICANT RISK OF AGRANULOCYTOSIS, A POTENTIALLY LIFE-THREATENING ADVERSE EVENT (SEE BELOW), CLOZARIL SHOULD BE RESERVED FOR USE IN THE TREATMENT OF SEVERELY ILL SCHIZOPHRENIC PATIENTS WHO FAIL TO SHOW AN ACCEPTABLE RESPONSE TO ADEQUATE COURSES OF STANDARD ANTIPSYCHOTIC DRUG TREATMENT, EITHER BECAUSE OF INSUFFICIENT EFFECTIVENESS OR THE INABILITY TO ACHIEVE AN EFFECTIVE DOSE DUE TO INTOLERABLE ADVERSE EFFECTS FROM THOSE DRUGS. CONSEQUENTLY, BEFORE INITIATING TREATMENT WITH CLOZARIL, IT IS STRONGLY RECOMMENDED THAT A PATIENT BE GIVEN AT LEAST TWO TRIALS, EACH WITH A DIFFERENT STANDARD ANTIPSYCHOTIC DRUG PRODUCT, AT AN ADEQUATE DOSE AND FOR AN ADEQUATE DURATION.

PATIENTS WHO ARE BEING TREATED WITH CLOZARIL MUST HAVE A BASELINE WHITE BLOOD CELL (WBC) AND DIFFERENTIAL COUNT BEFORE INITIATION OF TREATMENT, AND A WBC COUNT EVERY WEEK THROUGHOUT TREATMENT, AND FOR FOUR WEEKS AFTER THE DISCONTINUATION OF CLOZARIL.

CLOZARIL IS AVAILABLE ONLY THROUGH THE CLOZARIL PATIENT MANAGEMENT SYSTEM™ (CPMS™).

##### Agranulocytosis

Agranulocytosis, defined as a granulocyte count (polys + bands) of less than 500 per mm<sup>3</sup>, has been estimated to occur in association with CLOZARIL use at a cumulative incidence at one year of approximately 1.3%, based on the occurrence of 15 U.S. cases out of 1743 patients exposed to CLOZARIL during its clinical testing prior to domestic marketing. All of these cases occurred at a time when the need for close monitoring of WBC counts was already recognized. This reaction could prove fatal if not detected early and therapy interrupted. While no fatalities have been associated with the U.S. agranulocytosis cases, and all cases have recovered fully, the U.S. sample is too small to reliably estimate the case fatality rate. Of the 112 cases of agranulocytosis reported worldwide in association with CLOZARIL use as of December 31, 1986, 35% were fatal. However, few of these deaths occurred since 1977, at which time the knowledge of CLOZARIL-induced agranulocytosis became more widespread, and close monitoring of WBC counts more widely practiced. Nevertheless, it is unknown at present what the case fatality rate will be for CLOZARIL-induced agranulocytosis, despite strict adherence to the recommendation for weekly monitoring of WBC counts.

Treatment should not be initiated if the WBC count is less than 3500 per mm<sup>3</sup>, or if the patient has a history of a myeloproliferative disorder, or previous CLOZARIL-induced agranulocytosis or granulocytopenia. Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat or any other signs of infection. If, after the initiation of treatment, the total WBC count has dropped below 3500 per mm<sup>3</sup> or it has dropped by a substantial amount from baseline, even if the count is above 3500 per mm<sup>3</sup>, or if immature forms are present, a repeat WBC count and a differential count should be done. If subsequent WBC counts and the differential count reveal a total WBC count between 3000 and 3500 per mm<sup>3</sup> and a granulocyte count above 1500 per mm<sup>3</sup>, twice weekly WBC counts and differential counts should be performed.

If the total WBC count falls below 3000 per mm<sup>3</sup> or the granulocyte count below 1500 per mm<sup>3</sup>, CLOZARIL therapy should be interrupted and patients should be carefully monitored for flu-like symptoms or other symptoms suggestive of infection. CLOZARIL therapy may be resumed if no symptoms of infection develop, and if the total WBC count returns to levels above 3000 per mm<sup>3</sup> and the granulocyte count returns to levels above 1500 per mm<sup>3</sup>. However, in this event, twice-weekly WBC counts and differential counts should continue until total WBC counts return to levels above 3500 per mm<sup>3</sup>.

If the total WBC count falls below 2000 per mm<sup>3</sup> or the granulocyte count falls below 1000 per mm<sup>3</sup>, bone marrow aspiration should be considered to ascertain granulopoietic status. Protective isolation with close observation may be indicated if granulopoiesis is determined to be deficient. Should evidence of infection develop, the patient should have appropriate cultures performed and an appropriate antibiotic regimen instituted.

Patients whose total WBC counts fall below 2000 per mm<sup>3</sup>, or granulocyte counts below 1000 per mm<sup>3</sup> during CLOZARIL therapy should *not* be re-challenged with CLOZARIL. Patients discontinued from CLOZARIL therapy due to significant WBC suppression have been found to develop agranulocytosis upon re-challenge, often with a shorter latency on re-exposure. To reduce the chances of re-challenge occurring in patients who have experienced significant bone marrow suppression during CLOZARIL therapy, a single, national master file will be maintained confidentially within the CPMS (Clozaril Patient Management System).

Except for evidence of significant bone marrow suppression during initial CLOZARIL therapy, there are no established risk factors, based on worldwide experience, for the development of agranulocytosis in association with CLOZARIL use. However, a disproportionate number of the U.S. cases of agranulocytosis occurred in patients of Jewish background compared to the overall proportion of such patients exposed during the domestic development of CLOZARIL. Most of the U.S. cases occurred within 4-10 weeks of exposure, but neither dose nor duration is a reliable predictor of this problem. No patient characteristics have been clearly linked to the development of agranulocytosis in association with CLOZARIL use, but agranulocytosis associated with other antipsychotic drugs has been reported to occur with a greater frequency in women, the elderly and in patients who are cachectic or have serious underlying medical illness; such patients may also be at particular risk with CLOZARIL.

To reduce the risk of agranulocytosis developing undetected, CLOZARIL will be dispensed only within the Clozaril Patient Management System.

##### Seizures

Seizure has been estimated to occur in association with CLOZARIL use at a cumulative incidence at one year of approximately 5%, based on the occurrence of one or more seizures in 61 of 1743 patients exposed to CLOZARIL during its clinical testing prior to domestic marketing (i.e., a crude rate of 3.5%). Dose appears to be an important predictor of seizure, with a greater likelihood of seizure at the higher CLOZARIL doses used.

Caution should be used in administering CLOZARIL to patients having a history of seizures or other predisposing factors. Because of the substantial risk of seizure associated with CLOZARIL use, patients should be advised not to engage in any activity where sudden loss of consciousness could cause serious risk to themselves or others, e.g., the operation of complex machinery, driving an automobile, swimming, climbing, etc.

##### Adverse Cardiovascular Effects

Orthostatic hypotension can occur with CLOZARIL treatment, especially during initial titration in association with rapid dose escalation, and may represent a continuing risk in some patients. Tachycardia, which may be sustained, has also been observed in approximately 25% of patients taking CLOZARIL, with patients having an average increase in pulse rate of 10-15 bpm. The sustained tachycardia is not simply a reflex response to hypotension, and is present in all positions monitored. Either tachycardia or hypotension may pose a serious risk for an individual with compromised cardiovascular function. A minority of CLOZARIL-treated patients experience ECG repolarization changes similar to those seen with other antipsychotic drugs, including S-T segment depression and flattening or inversion of T waves, which all normalize after discontinuation of CLOZARIL. The clinical significance of these changes is unclear. However, in clinical trials with CLOZARIL, several patients experienced significant cardiac events, including ischemic changes, myocardial infarction, nonfatal arrhythmias and sudden unexplained death. Causality assessment was difficult in many of these cases because of serious preexisting cardiac disease and plausible alternative causes. Rare instances of sudden, unexplained death have been reported in psychiatric patients, with or without associated antipsychotic drug treatment, and the relationship of these events to antipsychotic drug use is unknown. CLOZARIL should be used with caution in patients with known cardiovascular disease, and the recommendation for gradual titration of dose should be carefully observed.

##### Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperreflexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). No cases of NMS have been attributed to CLOZARIL alone. However, there have been several reported cases of NMS in patients treated concomitantly with lithium or other CNS-active agents.

##### Tardive Dyskinesia

A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of treatment, which patients are likely to develop the syndrome.

There are several reasons for predicting that CLOZARIL may be different from other antipsychotic drugs in its potential for inducing tardive dyskinesia, including the preclinical finding that it has a relatively weak dopamine blocking effect and the clinical finding of a virtual absence of certain acute extrapyramidal symptoms, e.g., dystonia. In addition, there have been no confirmed cases of tardive dyskinesia developing in association with CLOZARIL use. Nevertheless, it cannot yet be concluded, without more extended experience, that CLOZARIL is incapable of inducing this syndrome.

##### PRECAUTIONS

Because of the significant risk of agranulocytosis and seizure, both of which present a continuing risk over time, the extended treatment of patients failing to show an acceptable level of clinical response should ordinarily be avoided. In addition, the need for continuing treatment in patients exhibiting beneficial clinical responses should be periodically re-evaluated. During CLOZARIL therapy, patients may experience transient temperature elevations above 100.4°F (38°C), with the peak incidence within the first three weeks of treatment. While this fever is generally benign and self-limiting, it may necessitate discontinuing patients from treatment. On occasion, there may be an associated increase or decrease in WBC count. Patients with fever should be carefully evaluated to rule out the possibility of an underlying infectious process or the development of agranulocytosis. In the presence of high fever, the possibility of neuroleptic malignant syndrome (NMS) must be considered. CLOZARIL has very potent anticholinergic effects, and great care should be exercised in using this drug in the presence of prostatic enlargement or narrow angle glaucoma. Because of initial sedation, CLOZARIL may impair mental and/or physical abilities, especially during the first few days of therapy. The recommendations for gradual dose escalation should be carefully adhered to, and patients cautioned about activities requiring alertness. Clinical experience with CLOZARIL in patients with concomitant systemic diseases is limited. Nevertheless, caution is advisable in using CLOZARIL in patients with hepatic, renal or cardiac disease.

##### Information for Patients

Patients who are to receive CLOZARIL should be warned about the significant risk of developing agranulocytosis. They should be informed that weekly blood tests are required to monitor for the occurrence of agranulocytosis, and that CLOZARIL tablets will be made available only through a special program designed to ensure the required blood monitoring. Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat, malaise, mucous membrane ulceration or other possible signs of infection. Particular attention should be paid to any flu-like complaints or other symptoms that might suggest infection. Patients should be informed of the significant risk of seizure during CLOZARIL treatment, and they should be advised to avoid driving and any other potentially hazardous activity while taking CLOZARIL. Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration. Patients should notify their physician if they are taking, or plan to take, any prescription or over-the-counter drugs or alcohol. Patients should notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should not breast feed an infant if they are taking CLOZARIL.



**CLOZARIL®**

(clozapine)

TABLETS

**Drug Interactions**

The risks of using CLOZARIL in combination with other drugs have not been systematically evaluated. The mechanism of CLOZARIL-induced agranulocytosis is unknown; nonetheless, the possibility that causative factors may interact synergistically to increase the risk and/or severity of bone marrow suppression warrants consideration. Therefore, CLOZARIL should not be used with other agents having a well-known potential to suppress bone marrow function. Given the primary CNS effects of CLOZARIL, caution is advised in using it concomitantly with other CNS-active drugs. Because CLOZARIL is highly bound to serum protein, the administration of CLOZARIL to a patient taking another drug which is highly bound to protein (e.g., warfarin, digoxin) may cause an increase in plasma concentrations of these drugs, potentially resulting in adverse effects. Conversely, adverse effects may result from displacement of protein-bound CLOZARIL by other highly bound drugs.

CLOZARIL may also potentiate the hypotensive effects of antihypertensive drugs and the anticholinergic effects of atropine-type drugs. The administration of epinephrine should be avoided in the treatment of drug-induced hypotension because of a possible reverse epinephrine effect.

**Pregnancy Category B**

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, and in view of the desirability of keeping the administration of all drugs to a minimum during pregnancy, this drug should be used only if clearly needed.

**ADVERSE REACTIONS**

Adverse events observed in association with the use of CLOZARIL in clinical trials at an incidence of 5% or greater were: central nervous system complaints, including drowsiness/sedation, dizziness/vertigo, headache and tremor; autonomic nervous system complaints, including salivation, sweating, dry mouth and visual disturbances; cardiovascular findings, including tachycardia, hypotension and syncope; and gastrointestinal complaints, including constipation and nausea; and fever. Complaints of drowsiness/sedation tend to subside with continued therapy or dose reduction. Salivation may be profuse, especially during sleep, but may be diminished with dose reduction.

**DOSAGE AND ADMINISTRATION****Initial Treatment**

It is recommended that treatment with CLOZARIL begin at 25 mg once or twice daily, and then be continued with daily dosage increments of 25 to 50 mg/day, if well-tolerated, to achieve a target dose of 300 to 450 mg/day by the end of two weeks. Subsequent dosage increments should be made no more than once- or twice-weekly, in increments not to exceed 100 mg. Cautious titration and a divided dosage schedule are necessary to minimize the risks of hypotension, seizure, and sedation.

**Therapeutic Dose Adjustment**

Daily dosing should continue on a divided basis as an effective and tolerable dose level is sought. While many patients may respond adequately at doses between 300-600 mg/day, it may be necessary to raise the dose to the 600-900 mg/day range to obtain an acceptable response. [Note: In the multicenter study providing the primary support for the superiority of CLOZARIL in treatment resistant patients, the mean and median CLOZARIL doses were both approximately 600 mg/day.]

Because of the possibility of increased adverse reactions at higher doses, particularly seizures, patients should ordinarily be given adequate time to respond to a given dose level before escalation to a higher dose is contemplated.

Dosing should not exceed 900 mg/day.

**Discontinuation of Treatment**

In the event of planned termination of CLOZARIL therapy, gradual reduction in dose is recommended over a 1 to 2 week period. However, should a patient's medical condition require abrupt discontinuation (e.g., leukopenia), the patient should be carefully observed for the recurrence of psychotic symptoms.

CLOZARIL is available only through the Clozaril Patient Management System, a program that combines white blood cell testing, patient monitoring, pharmacy, and drug distribution services, all linked to compliance with required safety monitoring.

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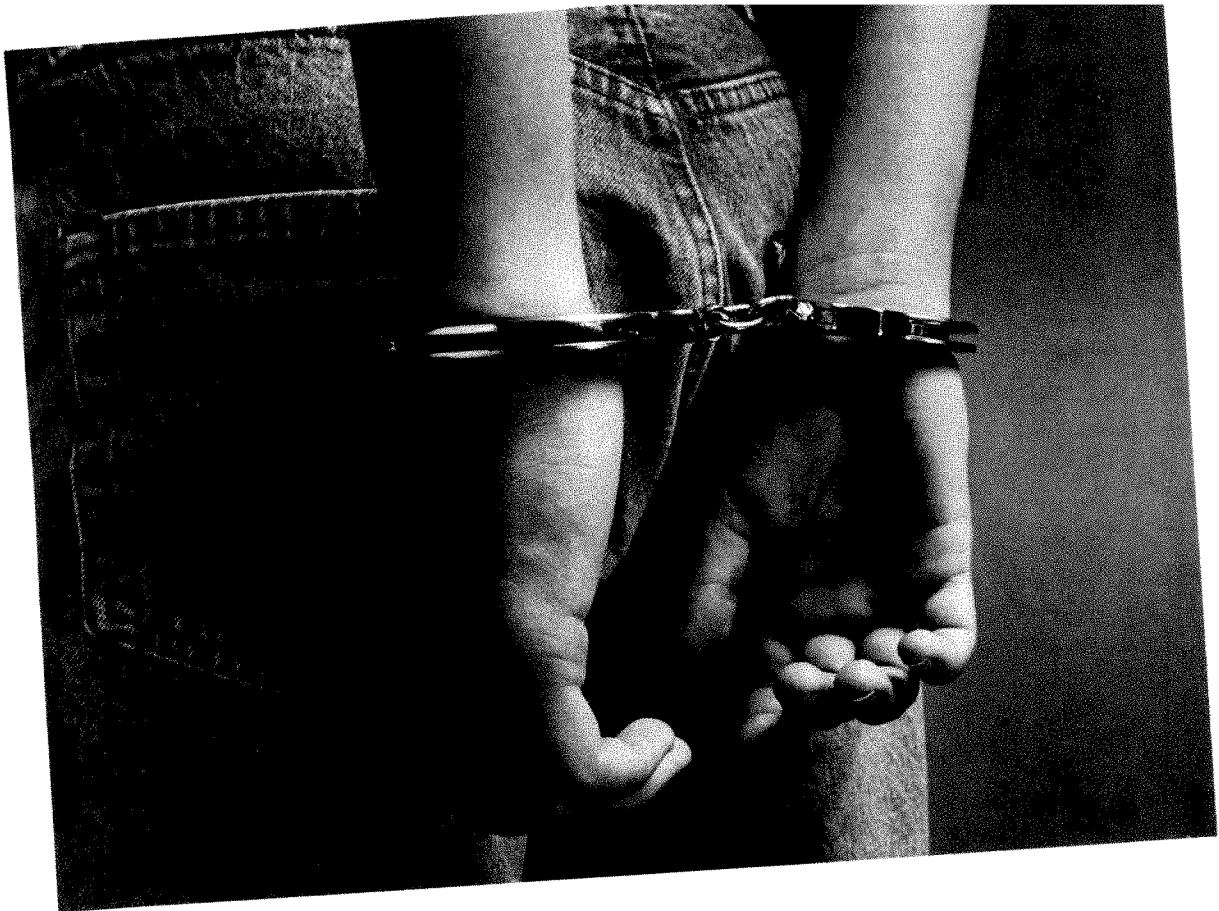
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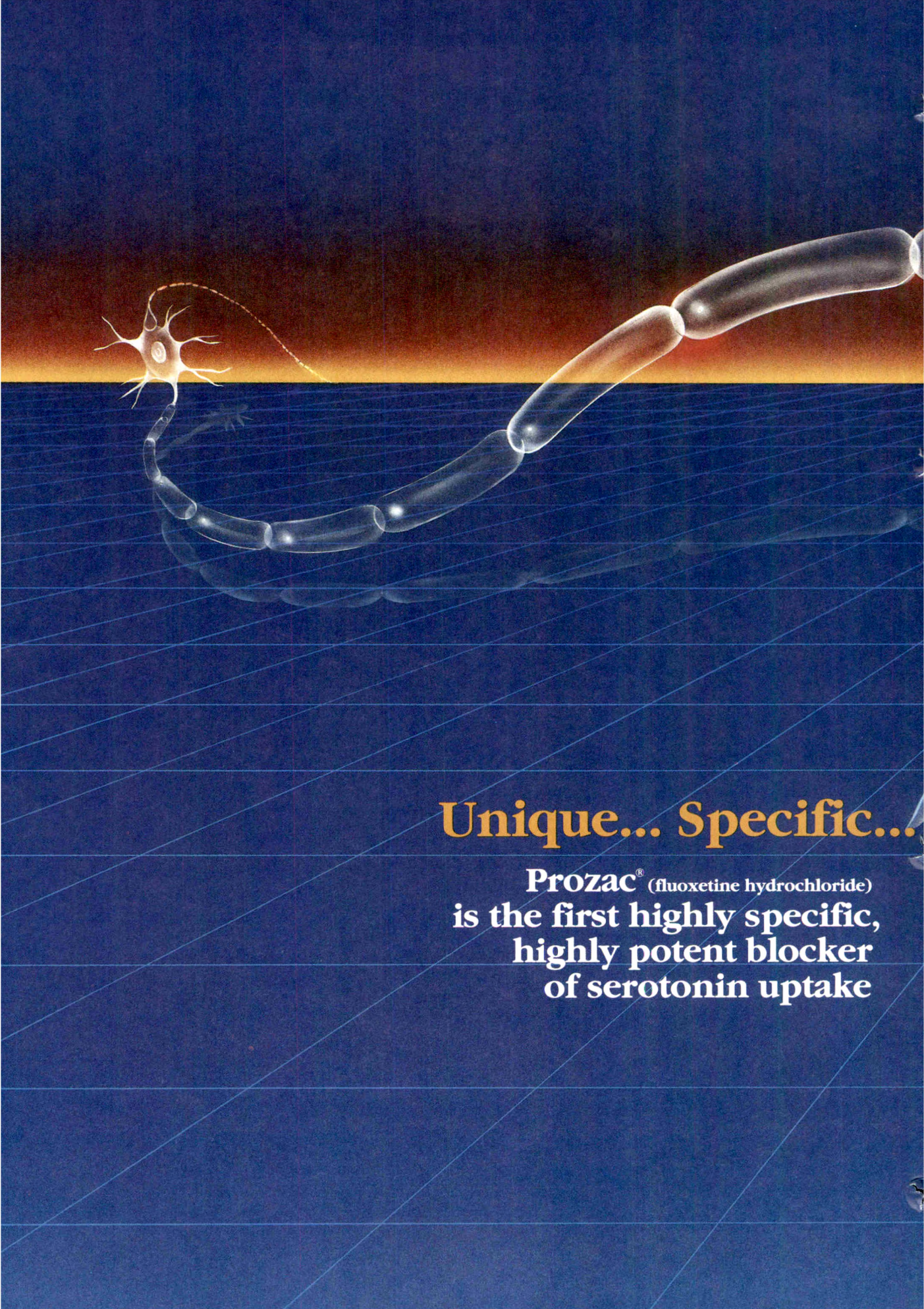
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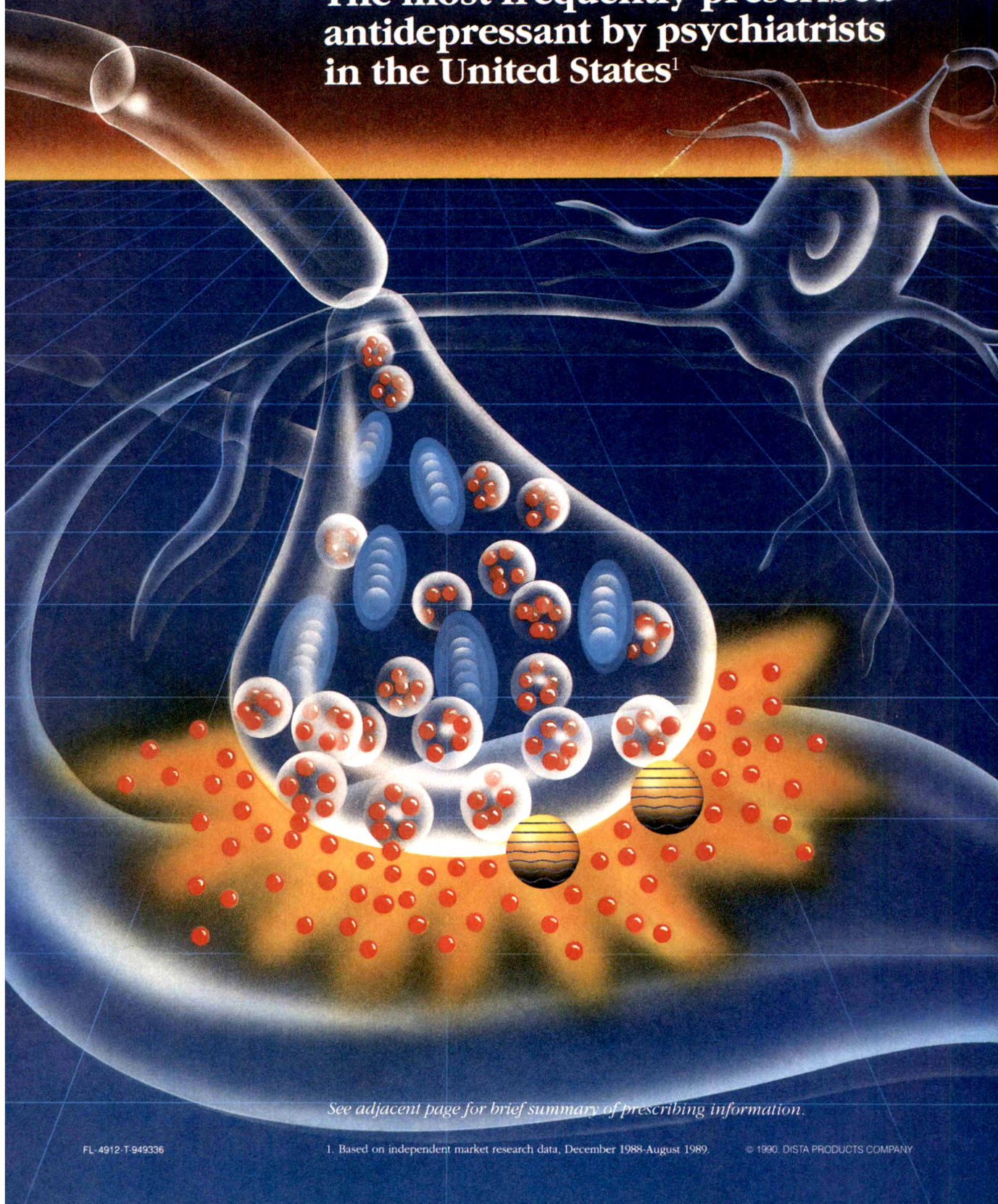
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antidepressant by psychiatrists  
in the United States<sup>1</sup>**



*See adjacent page for brief summary of prescribing information.*



## Prozac® (fluoxetine hydrochloride)

### Brief Summary:

Consult the package literature for complete information.

**Indications:** Prozac is indicated for the treatment of depression.

**Contraindication:** Prozac is contraindicated in patients known to be hypersensitive to it.

**Warnings: Monoamine Oxidase Inhibitors**—Data on the effects of the combined use of fluoxetine and MAO inhibitors are limited. Their combined use should be avoided. Based on experience with the combined administration of MAOIs and tricyclics, at least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with fluoxetine.

Because of the long half-lives of fluoxetine and its active metabolite, at least five weeks (approximately five half-lives of norfluoxetine) should elapse between discontinuation of fluoxetine and initiation of therapy with an MAOI. Administration of an MAOI within five weeks of discontinuation of fluoxetine may increase the risk of serious events. While a causal relationship to fluoxetine has not been established, death has been reported to occur following the initiation of MAOI therapy shortly after discontinuation of fluoxetine.

**Rash and Allergic Reactions**—During premarketing testing of more than 5,600 US patients given fluoxetine, approximately 4% developed a rash and/or urticaria. Among these cases, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

Two patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but one was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was considered variously to be a vasculitis or erythema multiforme. Several other patients have had systemic syndromes suggestive of serum sickness.

Since the introduction of Prozac, systemic events, possibly related to vasculitis, have developed in patients with rash. Although these events are rare, they may be serious, involving the lung, kidney, or liver. Death has been reported to occur in association with these systemic events.

Whether these systemic events and rash have a common underlying cause or are due to different etiologies or pathogenic processes is not known. Upon the appearance of rash, Prozac should be discontinued.

**Precautions: General—Anxiety and Insomnia**—Anxiety, nervousness, and insomnia were reported by 10% to 15% of patients treated with Prozac. These symptoms led to drug discontinuation in 5% of patients treated with Prozac.

**Altered Appetite and Weight**—Significant weight loss, especially in underweight depressed patients, may be an undesirable result of treatment with Prozac.

In controlled clinical trials, approximately 9% of patients treated with Prozac experienced anorexia. This incidence is approximately sixfold that seen in placebo controls. A weight loss of greater than 5% of body weight occurred in 13% of patients treated with Prozac compared to 4% of placebo- and 3% of tricyclic-antidepressant-treated patients. However, only rarely have patients been discontinued from treatment with Prozac because of weight loss.

**Activation of Mania/Hypomania**—During premarketing testing, hypomania or mania occurred in approximately 1% of fluoxetine-treated patients. Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed antidepressants.

**Seizures**—Twelve patients among more than 6,000 evaluated worldwide in the course of premarketing development of fluoxetine experienced convulsions (or events described as possibly having been seizures), a rate of 0.2% that appears to be similar to that associated with other marketed antidepressants. Prozac should be introduced with care in patients with a history of seizures.

**Suicide**—The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for Prozac should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

**The Long Elimination Half-Lives of Fluoxetine and Its Metabolites**—Because of the long elimination half-lives of the parent drug (two to three days) and its major active metabolite (seven to nine days), changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment (See Clinical Pharmacology and Dosage and Administration).

**Use in Patients With Concomitant Illness**—Clinical experience with Prozac in patients with concomitant systemic illness is limited. Caution is advisable in using Prozac in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Fluoxetine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from clinical studies during the product's premarketing testing. However, the electrocardiograms of 312 patients who received Prozac in double-blind trials were retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed. The mean heart rate was reduced by approximately three beats/min.

In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A lower or less frequent dose should be used in patients with cirrhosis.

Since fluoxetine is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. However, until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with fluoxetine, it should be used with caution in such patients.

In patients with diabetes, Prozac may alter glycemic control. Hypoglycemia has occurred during therapy with Prozac, and hyperglycemia has developed following discontinuation of the drug. As is true with many other types of medication when taken concurrently by patients with diabetes, insulin and/or oral hypoglycemic dosage may need to be adjusted when therapy with Prozac is instituted or discontinued.

**Interference With Cognitive and Motor Performance**—Any psychoactive drug may impair judgment, thinking, or motor skills, and patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely.

**Information for Patients**—Physicians are advised to discuss the following issues with patients for whom they prescribe Prozac:

Because Prozac may impair judgment, thinking, or motor skills, patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected.

Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs or alcohol.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast feeding an infant.

Patients should be advised to notify their physician if they develop a rash or hives.

**Laboratory Tests**—There are no specific laboratory tests recommended.

**Drug Interactions**—As with all drugs, the potential for interaction by a variety of mechanisms (ie, pharmacodynamic, pharmacokinetic drug inhibition or enhancement, etc) is a possibility (See Accumulation and Slow Elimination under Clinical Pharmacology).

**Tryptophan**—Five patients receiving Prozac in combination with tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress.

**Monoamine Oxidase Inhibitors**—See Warnings.

**Other Antidepressants**—There have been greater than twofold increases of previously stable plasma levels of other antidepressants when Prozac has been administered in combination with these agents (See Accumulation and

Slow Elimination under Clinical Pharmacology).

**Lithium**—There have been reports of both increased and decreased lithium levels when lithium was used concomitantly with fluoxetine. Cases of lithium toxicity have been reported. Lithium levels should be monitored when these drugs are administered concomitantly.

**Diazepam Clearance**—The half-life of concurrently administered diazepam may be prolonged in some patients (See Accumulation and Slow Elimination under Clinical Pharmacology).

**Potential Effects of Coadministration of Drugs Highly Bound to Plasma Protein**—Because fluoxetine is highly bound to plasma protein, the administration of fluoxetine to a patient taking another drug that is tightly bound to protein (eg, Coumadin, digoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein-bound fluoxetine by other tightly bound drugs (See Accumulation and Slow Elimination under Clinical Pharmacology).

**CNS-Active Drugs**—The risk of using Prozac in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of Prozac and such drugs is required (See Accumulation and Slow Elimination under Clinical Pharmacology).

**Electroconvulsive Therapy**—There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. A single report of a prolonged seizure in a patient on fluoxetine has been reported.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**—There is no evidence of carcinogenicity, mutagenicity, or impairment of fertility with Prozac.

The dietary administration of fluoxetine to rats and mice for two years at levels equivalent to approximately 7.5 and 9.0 times the maximum human dose (80 mg) respectively produced no evidence of carcinogenicity.

Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Two fertility studies conducted in rats at doses of approximately five and nine times the maximum human dose (80 mg) indicated that fluoxetine had no adverse effects on fertility. A slight decrease in neonatal survival was noted, but this was probably associated with depressed maternal food consumption and suppressed weight gain.

**Pregnancy—Teratogenic Effects—Pregnancy Category B**—Reproduction studies have been performed in rats and rabbits at doses nine and 11 times the maximum daily human dose (80 mg) respectively and have revealed no evidence of harm to the fetus due to Prozac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

**Labor and Delivery**—The effect of Prozac on labor and delivery in humans is unknown.

**Nursing Mothers**—Because many drugs are excreted in human milk, caution should be exercised when Prozac is administered to a nursing woman. In one breast milk sample, the concentration of fluoxetine plus norfluoxetine was 70.4 ng/mL. The concentration in the mother's plasma was 295.0 ng/mL. No adverse effects on the infant were reported.

**Usage in Children**—Safety and effectiveness in children have not been established.

**Usage in the Elderly**—Prozac has not been systematically evaluated in older patients; however, several hundred elderly patients have participated in clinical studies with Prozac, and no unusual adverse age-related phenomena have been identified. However, these data are insufficient to rule out possible age-related differences during chronic use, particularly in elderly patients who have concomitant systemic illnesses or who are receiving concomitant drugs.

**Hyponatremia**—Several cases of hyponatremia (some with serum sodium lower than 110 mEq/L) have been reported. The hyponatremia appeared to be reversible when Prozac was discontinued. Although these cases were complex with varying possible etiologies, some were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these occurrences have been in older patients and in patients taking diuretics or who were otherwise volume depleted.

**Adverse Reactions: Commonly Observed**—The most commonly observed adverse events associated with the use of Prozac and not seen at an equivalent incidence among placebo-treated patients were: nervous system complaints, including anxiety, nervousness, and insomnia; drowsiness and fatigue or asthenia; tremor; sweating; gastrointestinal complaints, including anorexia, nausea, and diarrhea; and dizziness or lightheadedness.

**Associated With Discontinuation of Treatment**—Fifteen percent of approximately 4,000 patients who received Prozac in US premarketing clinical trials discontinued treatment due to an adverse event. The more common events causing discontinuation included: psychiatric (5.3%), primarily nervousness, anxiety, and insomnia; digestive (3.0%), primarily nausea; nervous system (1.6%), primarily dizziness; body as a whole (1.5%), primarily asthenia and headache; and skin (1.4%), primarily rash and pruritus.

**Incidence in Controlled Clinical Trials**—The table that follows enumerates adverse events that occurred at a frequency of 1% or more among Prozac-treated patients who participated in controlled trials comparing Prozac with placebo. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nongdrug factors to the side-effect incidence rate in the population studied.

TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS					
Body System/ Adverse Event*	Percentage of Patients Reporting Event†		Body System/ Adverse Event*	Percentage of Patients Reporting Event†	
	Prozac (N = 1,735)	Placebo (N = 739)		Prozac (N = 1,735)	Placebo (N = 739)
<b>Nervous</b>	20.3	15.5	<b>Body as a Whole</b>	4.4	1.9
Headache	14.9	8.2	Infection, viral	3.4	3.1
Nervousness	13.6	7.1	Pain, limb	1.6	1.1
Insomnia	13.6	5.3	Fever	1.3	1.1
Drowsiness	9.4	3.5	Pain, chest	1.3	1.1
Anxiety	7.9	2.4	Allergy	1.2	1.1
Tremor	5.7	3.3	Influenza	1.2	1.5
Dizziness	5.7	1.1	<b>Respiratory</b>		
Fatigue	1.9	1.3	Cough	7.6	6.0
Sedated	1.7	2.0	Flu-like syndrome	2.8	1.9
Sensation disturbance	1.6	—	Pharyngitis	2.7	1.3
Lightheadedness	1.6	—	Nasal congestion	2.6	2.3
Libido, decreased	1.5	—	Headache, tension	2.3	1.8
<b>Digestive</b>			Sinusitis	2.1	2.0
Nausea	21.1	10.1	Cough	1.5	1.6
Diarrhea	12.3	7.0	Dysnea	1.4	—
Mouth dryness	9.5	6.0	<b>Cardiovascular</b>		
Anorexia	8.7	1.5	Hot flushes	1.8	1.0
Dyspepsia	6.4	4.3	Palpitations	1.3	1.4
Constipation	4.5	3.3	<b>Musculoskeletal</b>		
Pain, abdominal	3.4	2.9	Pain, back	2.0	2.4
Vomiting	2.4	1.3	Pain, joint	1.2	1.1
Taste change	1.8	—	Pain, muscle	1.2	1.0
Flatulence	1.6	—	<b>Urogenital</b>		
Gastroenteritis	1.0	1.4	Urinary tract infection	1.9	1.4
<b>Skin and Appendages</b>			Sexual dysfunction	1.9	—
Sweating excessive	8.4	3.8	Frequent micturition	1.6	—
Rash	2.7	1.4	Urinary tract infection	1.2	—
Pruritus	2.4	—	<b>Special Senses</b>		
			Vision disturbance	2.8	1.8

\*Events reported by at least 1% of Prozac-treated patients are included.  
†Incidence less than 1%.

**Other Events Observed During the Premarketing Evaluation of Prozac**—During clinical testing in the US, multiple doses of Prozac were administered to approximately 5,600 subjects. Unwanted events associated with this exposure were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of unwanted events into a limited (ie, reduced) number of standardized event categories.

In the tabulations which follow, a standard COSTART Dictionary terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the 5,600 individuals exposed to Prozac who experienced an event of the type cited on at least one occasion while receiving Prozac. All reported events are included except those already listed in tables, those COSTART terms so general as to be uninformative, and those events where a drug cause was remote. It is important to emphasize that, although the events reported did occur during treatment with Prozac, they were not necessarily caused by it.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

**Body as a Whole—Frequent:** chills; **Infrequent:** chills and fever, cyst, face edema, hanger effect, jaw pain, malaise, neck pain, neck rigidity, and pelvic pain; **Rare:** abdomen enlarged, cellulitis, hydrocephalus, hypothermia, LE syndrome, moniliasis, and serum sickness.

**Cardiovascular System—Infrequent:** angina pectoris, arrhythmia, hemorrhage, hypertension, hypotension, migraine, postural hypotension, syncope, and tachycardia; **Rare:** AV block first-degree, bradycardia, bundle-branch block, cerebral ischemia, myocardial infarct, thrombophlebitis, vascular headache, and ventricular arrhythmia.

**Digestive System—Frequent:** increased appetite; **Infrequent:** aphthous stomatitis, dysphagia, eructation, esophagitis, gastritis, gingivitis, glossitis, liver function tests abnormal, melena, stomatitis, thirst; **Rare:** bloody diarrhea, cholecystitis, cholelithiasis, colitis, duodenal ulcer, enteritis, fecal incontinence, hematemesis, hepatitis, hepatomegaly, hyperchlorhydria, increased salivation, jaundice, liver tenderness, mouth ulceration, salivary gland enlargement, stomach ulcer, tongue discoloration, and tongue edema.

**Endocrine System—Infrequent:** hypothyroidism; **Rare:** goiter and hyperthyroidism.

**Hemic and Lymphatic System—Infrequent:** anemia and lymphadenopathy; **Rare:** bleeding time increased, blood dyscrasia, leukopenia, lymphocytosis, petechia, purpura, sedimentation rate increased, and thrombocytopenia.

**Metabolic and Nutritional—Frequent:** weight loss; **Infrequent:** generalized edema, hypoglycemia, peripheral edema, and weight gain; **Rare:** dehydration, gout, hypercholesterolemia, hyperglycemia, hyperlipemia, hypoglycemic reaction, hypokalemia, hyponatremia, and iron deficiency anemia.

**Musculoskeletal System—Infrequent:** arthritis, bone pain, bursitis, tenosynovitis, and twitching; **Rare:** bone necrosis, chondrodystrophy, muscle hemorrhage, myositis, osteoporosis, pathological fracture, and rheumatoid arthritis.

**Nervous System—Frequent:** abnormal dreams and agitation; **Infrequent:** abnormal gait, acute brain syndrome, akathisia, amnesia, apathy, ataxia, buccoglossal syndrome, CNS stimulation, convulsion, delusions, depersonalization, emotional lability, euphoria, hallucinations, hostility, hyperkinesia, hypesthesia, incoordination, libido increased, manic reaction, neuralgia, neuropathy, paranoid reaction, psychosis, and vertigo; **Rare:** abnormal electroencephalogram, antisocial reaction, chronic brain syndrome, circumoral paresthesia, CNS depression, coma, dysarthria, dystonia, extrapyramidal syndrome, hypertension, hysteria, myoclonus, nystagmus, paralysis, reflexes decreased, stupor, and torticollis.

**Respiratory System—Frequent:** bronchitis, rhinitis, and yawn; **Infrequent:** asthma, cystitis, hiccup, hyperventilation, and pneumonia; **Rare:** apnea, hemoptysis, hypoxia, larynx edema, lung edema, lung fibrosis/alveolitis, and pleural effusion.

**Skin and Appendages—Infrequent:** acne, alopecia, contact dermatitis, dry skin, herpes simplex, maculopapular rash, and urticaria; **Rare:** eczema, erythema multiforme, fungal dermatitis, herpes zoster, hirsutism, psoriasis, purpuric rash, pustular rash, seborrhea, skin discoloration, skin hypertrophy, subcutaneous nodule, and vesiculobullous rash.

**Special Senses—Infrequent:** amblyopia, conjunctivitis, ear pain, eye pain, mydriasis, photophobia, and tinnitus; **Rare:** blepharitis, cataract, corneal lesion, deafness, diplopia, eye hemorrhage, glaucoma, iritis, ptosis, strabismus, and taste loss.

**Urogenital System—Infrequent:** abnormal ejaculation, amenorrhea, breast pain, cystitis, dysuria, fibrocystic breast, impotence, leukorrhea, menopause, menorrhagia, ovarian disorder, urinary incontinence, urinary retention, urinary urgency, urination impaired, and vaginitis; **Rare:** abortion, albuminuria, breast enlargement, dyspareunia, epididymitis, female lactation, hematuria, hypomenorrhea, kidney calculus, metrorrhagia, orchitis, polyuria, pyelonephritis, pyuria, salpingitis, urethral pain, urethritis, urinary tract disorder, urolithiasis, uterine hemorrhage, uterine spasm, and vaginal hemorrhage.

**Postintroduction Reports**—Voluntary reports of adverse events temporarily associated with Prozac that have been received since market introduction and which may have no causal relationship with the drug include the following: vaginal bleeding after drug withdrawal, hyperprolactinemia, thrombocytopenia, and confusion.

**Overdose: Human Experience**—As of December 1987, there were two deaths among approximately 38 reports of acute overdose with fluoxetine, either alone or in combination with other drugs and/or alcohol. One death involved a combined overdose with approximately 1,800 mg of fluoxetine and an undetermined amount of meprobamate. Plasma concentrations of fluoxetine and meprobamate were 4.57 mg/L and 4.18 mg/L respectively. A second death involved three drugs yielding plasma concentrations as follows: fluoxetine, 1.93 mg/L; norfluoxetine, 1.10 mg/L; codeine, 1.80 mg/L; temazepam, 3.80 mg/L.

One other patient who reportedly took 3,000 mg of fluoxetine experienced two grand mal seizures that remitted spontaneously without specific anti-convulsant treatment (See Management). The actual amount of drug absorbed may have been less due to vomiting.

Nausea and vomiting were prominent in overdoses involving higher fluoxetine doses. Other prominent symptoms of overdose included agitation, restlessness, hypomania, and other signs of CNS excitation. Except for the two deaths noted above, all other overdose cases recovered without residua.

Since introduction, a single death attributed to overdose of fluoxetine alone has been reported.

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Additional information available to the profession on request.



**Dista Products Company**  
Division of Eli Lilly and Company  
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# Psychiatry Today

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## BREAKTHROUGH FOR THOUSANDS OF PROBLEM SCHIZOPHRENIC PATIENTS AND THEIR PSYCHIATRISTS

### Sandoz Introduces CLOZARIL® (clozapine) — A Breakthrough Antipsychotic Agent

For Patients Who Fail to Respond Adequately to Treatment With  
Appropriate Courses of Standard Antipsychotic Drugs

Sandoz Pharmaceuticals Corporation has announced the introduction of CLOZARIL (clozapine), a new, atypical antipsychotic agent that has demonstrated efficacy against symptoms of schizophrenia in severely ill ("problem") patients who fail to respond adequately to treatment with appropriate courses of standard antipsychotic drugs. The drug, whose pharmacologic profile suggests a unique mode of action, is being hailed as the first breakthrough in antipsychotic therapy in more than two decades. In a clinical trial, as reported by John Kane, MD, and others in an original article published in *Archives of General Psychiatry*, September 1988, CLOZARIL (clozapine) proved sig-

nificantly more effective than chlorpromazine in controlling both the positive and negative symptoms of chronic schizophrenia.

"CLOZARIL poses a very exciting opportunity," said John Kane, MD, chairman of the department of psychiatry, Hillside Hospital—Long Island Jewish Medical Center, and a key CLOZARIL investigator. "Our multicenter study suggests that the drug may be an important therapeutic advance in the treatment of schizophrenia." Other investigators have reported similar successes with CLOZARIL (clozapine) in many severely ill ("problem") schizophrenics who failed to respond adequately to treatment with

(Continued on page 3)

### Haloperidol Failures Respond

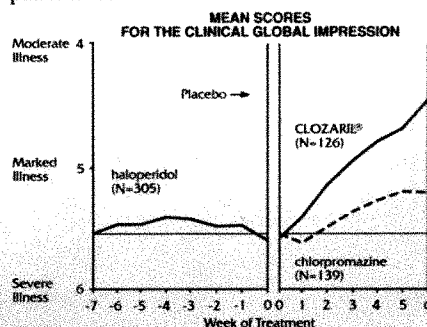
Chronic schizophrenics who had failed to respond to a six-week course of haloperidol showed significant improvement with CLOZARIL® therapy in the landmark multicenter clinical trial. Symptoms began to improve within two weeks after CLOZARIL therapy was begun. Improvement continued throughout the course of the study.

Study subjects were selected on the basis of a history of failure to respond to standard antipsychotic therapy. Prospective criteria included treatment failure on at least 60 mg/day of haloperidol. After six weeks, only 1.6% of the patients treated with haloperidol had responded positively. Others failed to respond or were not able to tolerate the drug.

When treated with CLOZARIL (clozapine), haloperidol nonresponders demonstrated significant improvement in a broad range of symptoms on the Brief Psychiatric Rating Scale (BPRS), including the positive symptom cluster of thought disturbances: hallucinations, unusual thought content, grandiosity and conceptual disorganization.

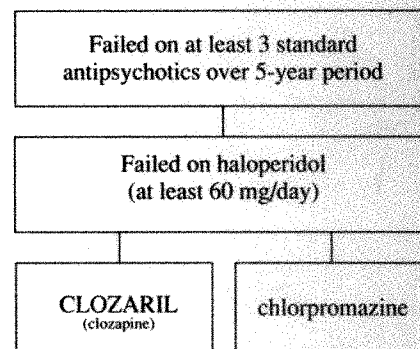
Many CLOZARIL-treated patients were rated significantly improved in the negative symptom cluster of anergia. The initial response to CLOZARIL therapy was dramatic and achieved statistical significance after only two weeks of treatment.

Researchers concluded that some 30% of CLOZARIL-treated patients showed significant improvement in overall clinical condition in only six weeks. Similar results were seen in only 4% of chlorpromazine-treated patients. ■



### Rigorous Study Shows Superior Efficacy

In a landmark U.S. multicenter trial, CLOZARIL® (clozapine) proved to have greater efficacy than chlorpromazine in problem schizophrenics who had previously failed on haloperidol.



According to Dr. Kane, the unusual protocol of the CLOZARIL trial had few precedents. "Many people thought this was an inordinately conservative test that really stacked the deck against clozapine," the investigator said.

Patients were first selected on the basis of a history of failure to respond to at least three drugs from two antipsychotic classes over the previous five years. They were then treated with at least 60 mg/day of haloperidol and 6 mg/day of benztrapine for up to six weeks. Patients who failed to respond were randomized into two groups — one treated with CLOZARIL (clozapine) and one with chlorpromazine plus benztrapine. Prophylactic benztrapine was employed in the chlorpromazine group to mask extrapyramidal side effects and help maintain double-blind conditions. In this population of haloperidol failures, CLOZARIL (clozapine) demonstrated significant superiority over chlorpromazine in the treatment of positive and negative schizophrenic symptoms. ■



## Positive and Negative Symptoms Respond to CLOZARIL® (clozapine)

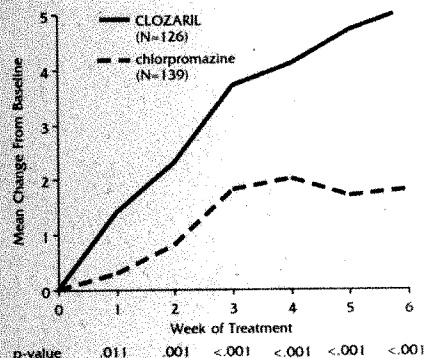
Dramatic evidence from a double-blind multicenter U.S. trial, published in the *Archives of General Psychiatry*, September 1988, indicates that CLOZARIL (clozapine) is effective against both "positive" and "negative" symptoms of schizophrenia in severely ill ("problem") patients who failed to respond adequately to treatment with appropriate courses of standard antipsychotic drugs. Within the first two weeks of CLOZARIL treatment, patients improved in several key areas of positive or florid symptomatology as measured on the Brief Psychiatric Rating Scale (BPRS): conceptual disorganization, suspiciousness, hallucinatory behavior, unusual thought content. CLOZARIL patients showed substantial improvement earlier and to a far greater degree than control patients treated with chlorpromazine.

Although the positive symptoms of schizophrenia have traditionally received the most clinical attention, there is growing

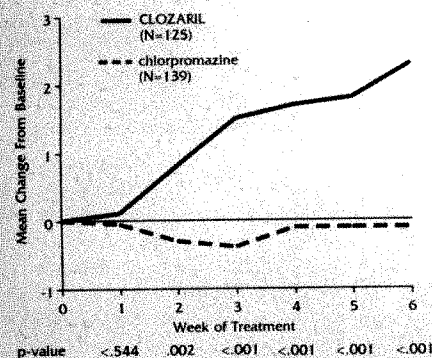
evidence that it is the negative or "deficit" symptoms of schizophrenia that cause much of the chronic disability in long-term patients. According to investigator Herbert Meltzer, MD, professor of psychiatry, Case Western Reserve University School of Medicine, "The really remarkable aspect of CLOZARIL has been its ability to deal with the deficit state, the apathy, lack of motivation and loss of social skills."

Patients treated with CLOZARIL (clozapine) for six weeks demonstrated significant improvement in a cluster of four key negative symptoms rated on the BPRS: emotional withdrawal, motor retardation, blunted affect and disorientation. Ratings of negative symptoms in patients in a control group treated with chlorpromazine remained unchanged. ■

### BRIEF PSYCHIATRIC RATING SCALE CLUSTER OF FOUR POSITIVE SYMPTOMS (conceptual disorganization, suspiciousness, hallucinatory behavior, unusual thought content)



### BRIEF PSYCHIATRIC RATING SCALE ANERGIA FACTOR



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## Patient Care Costs Down

The economic impact of schizophrenia is far greater than its actual incidence would suggest. Estimates of the cost of schizophrenia indicate that the mental health service costs alone range from \$11.6 billion to \$19.5 billion a year. Then there are the indirect costs, such as patients' lost income from inability to work, long-term disability payments, subsidies for housing and food, and hours of care devoted by family members.

A cost-effectiveness study by the Battelle Human Affairs Research Centers in Washington, D.C., found that CLOZARIL® therapy may impact favorably upon the tremendous costs of chronic schizophrenia. After two years of treatment with CLOZARIL (clozapine), costs of care for problem schizophrenic patients declined by nearly 31% according to the investigators.

The Battelle data were obtained from a retrospective study of 87 problem schizophrenic patients in seven psychiatric facilities. It was demonstrated that average annual costs of mental health services declined from \$80,440 per patient to \$55,867 in the second year of CLOZARIL therapy. During the second year of therapy, hospitalization costs averaged \$33,000 less per year for CLOZARIL patients than for those receiving standard antipsychotics. ■

## Unique Patient Management System Controls Blood Dyscrasia Risk

The risk of CLOZARIL®-induced agranulocytosis can now be effectively managed, investigators say, with the introduction of the Clozaril Patient Management System<sup>SM</sup> (CPMS<sup>SM</sup>), a comprehensive system of WBC testing, pharmacy, clinical laboratory and drug distribution services, all linked to compliance with required safety monitoring. CPMS<sup>SM</sup> utilizes the services of a national home healthcare company to monitor the white blood cell count of patients and to discontinue CLOZARIL (clozapine).

Although CLOZARIL (clozapine) produces fewer extrapyramidal side effects than standard antipsychotics, it has a higher risk of potentially fatal agranulocytosis. Current estimates indicate a 1-2% incidence for CLOZARIL (clozapine).

Worldwide use in the late 1970s convinced researchers that agranulocytosis could be recognized early. Fatalities declined sharply when clinicians became aware of the need to monitor white blood cell (WBC) counts and to discontinue clozapine as soon as a major drop in WBC count was detected. In U.S. clinical trials and compassionate use programs through mid-1989, agranulocytosis occurred in 15 of over 1,700 patients.

All cases were detected through WBC count monitoring; all reversed with discontinuation of therapy. There have been no deaths in the United States from CLOZARIL-associated agranulocytosis.

Because there are often no clinical signs of the onset of leukopenia, researchers say, mandatory weekly WBC counts are of critical importance in avoiding complications of agranulocytosis. With early detection, the WBC count will usually return to normal approximately two weeks after the drug is discontinued, reversing the condition. The goal of the mandatory monitoring system designed for CLOZARIL (clozapine) is to ensure that all patients donate a blood sample before receiving their weekly supply of the drug. Patient Case Administrators will alert psychiatrists to any changes in WBC status.

CPMS has been tested in pilot studies across the United States and has achieved over 99% blood monitoring compliance on the part of the patients — without interfering with the physician's medical control. ■



INTRODUCING

A BEACON OF  
**HOPE**

FOR THOUSANDS  
PROBLEM SCHIZOPHRENIC  
PATIENTS  
AND THEIR PSYCHIATRISTS






NEW  
**CLOZARIL**<sup>®</sup>  
(clozapine)

SUPERIOR  
ANTIPSYCHOTIC  
EFFICACY  
THAT  
GIVES HOPE  
FOR  
A  
NEW  
BEGINNING



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## HOPE BEGINS WITH SUPERIOR SYMPTOMATIC CONTROL\*

In a six-week controlled study in severely ill ("problem") schizophrenic patients who failed to respond adequately to treatment with appropriate courses of standard antipsychotic drugs:

- CLOZARIL® (clozapine) succeeded after standard antipsychotics, including haloperidol, failed
- Thirty percent of CLOZARIL patients experienced dramatic global improvement in only six weeks (as determined by the study's rigorous efficacy criteria) vs only 4% of patients receiving chlorpromazine
- Efficacy in both positive and negative symptomatology

## HOPE CONTINUES WITH A VIRTUAL ABSENCE OF CERTAIN ACUTE EXTRAPYRAMIDAL SYMPTOMS

- CLOZARIL® (clozapine) is indicated for patients intolerant of standard antipsychotics
- No confirmed cases of tardive dyskinesia in over 15 years' worldwide experience
- Side effects that have been reported include: agranulocytosis (1–2%), transient sedation (39%), hypersalivation (31%), tachycardia (25%), constipation (14%), hypotension (9%), hypertension (4%) and weight gain (4%)<sup>†</sup>
- CLOZARIL use is associated with a substantial risk of seizure, an apparently dose-dependent reaction affecting 1–2% of patients at low doses (below 300 mg/day), 3–4% at moderate doses, and 5% at high doses (600–900 mg/day)<sup>‡</sup>

## HOPE IS MAINTAINED THROUGH A MANDATORY WBC MONITORING SYSTEM WHICH HELPS MANAGE THE RISK OF AGRANULOCYTOSIS

- Agranulocytosis, a potentially fatal disorder, occurs in 1–2% of patients
- The Clozaril Patient Management System<sup>SM</sup> (CPMS<sup>SM</sup>) was created as an efficient means to detect developing agranulocytosis
- This structured weekly monitoring and drug delivery system helps to protect the patient and to support the physician

# CLOZARIL®

(clozapine)

25 mg and 100 mg tablets

**CLOZARIL therapy is available only through the Clozaril Patient Management System. Call 1-800-237-CPMS (2767) or mail in a completed CPMS patient enrollment form to prescribe CLOZARIL (clozapine). Contact your Sandoz Mental Health Sales Representative for general information on CLOZARIL (clozapine) and the Clozaril Patient Management System.**

\*In a double-blind study of CLOZARIL (clozapine) versus chlorpromazine encompassing 268 patients, all of whom had first failed on at least three standard antipsychotics over a five-year period and then on a trial of high-dose haloperidol.



INTRODUCING

# CLOZARIL<sup>®</sup>

(clozapine)

A BEACON OF  
HOPE  
FOR PROBLEM  
SCHIZOPHRENIC PATIENTS

To prescribe  
**CLOZARIL**  
(clozapine)  
call 1-800-237-CPMS (2767)  
or mail in a completed CPMS patient enrollment form.

†Tachycardia, hypotension and hypertension are the principal cardiovascular effects associated with CLOZARIL (clozapine).

‡Because of the substantial risk of seizure associated with CLOZARIL use, a dosage ceiling of 600 mg/day is recommended, although some patients may require up to 900 mg/day for a therapeutic effect.

HOPE  
FOR A NEW BEGINNING

**CLOZARIL<sup>®</sup>**

(clozapine)

25 mg and 100 mg tablets



**SANDOZ PHARMACEUTICALS**  
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# BREAKTHROUGH

(Continued from page 1)

appropriate courses of standard antipsychotic drugs. Herbert Meltzer, MD, Douglas Danford Bond Professor of Psychiatry at Case Western Reserve University School of Medicine, demonstrated the effect of 6-9 months' treatment with CLOZARIL® (clozapine) on social function and interpersonal relationships in 21 problem schizophrenic patients. According to Dr. Meltzer, "The extent of improvement in the QLS [Quality of Life Scale] scores after 6 months' clozapine treatment was impressive. Total QLS scores nearly tripled during this period. Total QLS scores at least doubled in 76% of the patients. The improvement was most marked in the area of ability to work or return to school, but was also strong in intrapsychic foundations and interpersonal relations."

The new drug has created considerable excitement among families of chronic schizophrenic patients. As one parent said, "For us, CLOZARIL (clozapine) means new hope, and that's been a scarce commodity among schizophrenic patients and their families."

Because of its unique pharmacologic profile, CLOZARIL (clozapine) is thought to have a somewhat different mode of action than standard antipsychotics. The new drug is characterized by a virtual absence of certain

acute extrapyramidal symptoms (e.g., dystonia). Also, unlike standard antipsychotics, it causes little or no elevation in serum prolactin levels and has not been linked to any confirmed cases of tardive dyskinesia.

However, it does carry an increased risk of seizure and agranulocytosis, necessitating weekly blood monitoring for all patients. The incidence of agranulocytosis, a potentially fatal disorder, associated with CLOZARIL (clozapine) is 1-2%. In Europe — principally before 1977 — prior to recognition and management of the risk, a number of fatalities occurred. With mandatory weekly white blood cell (WBC) monitoring, all cases in the United States through mid-1989 (15 in over 1,700 patients) have reversed, and no fatalities have occurred. ■

## Side Effects Profile Further Distinguishes CLOZARIL® (clozapine)

Because of its unique pharmacologic profile, CLOZARIL (clozapine) appears to have a more specific mechanism of action than standard antipsychotics. This may be the reason for the virtual absence of certain acute extrapyramidal side effects — and no confirmed cases of tardive dyskinesia. Researchers theorize that this is because the drug has been shown in animal studies to be more selective for dopamine receptors in the limbic area of the brain, rather than the striatal receptors affected by most standard antipsychotics. In addition, in both pre-clinical and clinical studies, CLOZARIL (clozapine) causes little or no elevation of serum prolactin levels, and thus tends not to produce prolactin-related side effects as do other antipsychotic drugs.

CLOZARIL (clozapine) is, however, associated with a higher incidence of agranulocytosis than standard antipsychotics — 1-2% as compared with 0.1% for standard agents. Careful monitoring through the Clozaril Patient Management System<sup>SM</sup> (CPMS<sup>SM</sup>) will help promote early detection and timely drug discontinuation. Other side effects that have been reported include transient sedation (39%), hypersalivation (31%), tachycardia (25%), constipation (14%), hypotension (9%), seizures (5%), hypertension (4%) and weight gain (4%).

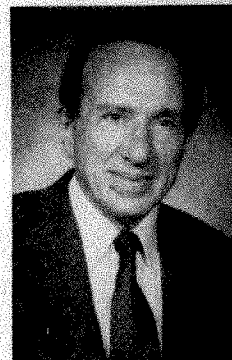
CLOZARIL use is associated with a substantial risk of seizure, an apparently dose-dependent reaction affecting 1-2% of patients at low doses (below 300 mg/day), 3-4% at moderate doses, and 5% at high doses (600-900 mg/day). In the multicenter

(Continued on page 4)

## CLOZARIL® Researcher Recounts CLOZARIL History

"I've seen CLOZARIL (clozapine) through its ups and downs," said Gilbert Honigfeld, PhD, associate director of Sandoz Research Institute, who has piloted the drug's development since joining Sandoz in 1973. Honigfeld recounted how the drug was first discovered in 1960 by Swiss scientists at the Wander Division of Sandoz and was being used in Europe in the 1970s when reports of agranulocytosis appeared.

These reports led to cessation of active U.S. CLOZARIL research for a number of years. "But clinicians would not let go of it," Honigfeld recalled. Patients were given the drug on a compassionate need basis, and evidence continued to mount that not only did CLOZARIL (clozapine) have superior efficacy, but that the risk of agranulocytosis could be managed with careful monitoring. Sandoz resumed clinical R&D in the '80s, and submitted results of its rigorous study in severely ill schizophrenic patients to government health officials in August 1987. ■



## Temple University Accredits CLOZARIL® Educational Program

Temple University has accredited the CLOZARIL Educational Program developed by Sandoz Pharmaceuticals Corporation to ensure safe and efficacious use of this new atypical antipsychotic agent. A series of teleconference workshops will be held at over 600 sites across the country. Physicians who participate will receive 4 hours of CME credit for attending the conference and completing the self-study materials.

These regional workshops will feature videotaped presentations and live interactive discussions via two-way telephone hookups. This will allow CLOZARIL investigators and other experts to answer audience questions on the spot. Psychiatrists and allied healthcare professionals attending the workshops will receive information about the benefits and risks of CLOZARIL therapy and the appropriate selection and management of patients.

Comprehensive take-home materials will include prescribing and product information, a psychiatrist's guide to CLOZARIL-associated agranulocytosis and a detailed description of the Clozaril Patient Management System<sup>SM</sup> (CPMS<sup>SM</sup>). ■

## Reimbursement

Efforts are being made to ensure that the majority of patients selected for CLOZARIL® therapy will be eligible to have their Clozaril Patient Management System<sup>SM</sup> (CPMS<sup>SM</sup>) costs reimbursed by third-party payers, such as state Medicaid programs and the Veterans Administration. Additionally, duration of hospitalization is expected to decrease for patients on CLOZARIL therapy. In one retrospective study, the time spent outside institutions increased from 44% before CLOZARIL treatment to 63% in the second year of treatment with CLOZARIL (clozapine). That results in significant savings in cost of care as former inpatients become outpatients. Around the country, enthusiasm is being expressed for the new medication, which is expected to reduce substantially the chronic care costs of schizophrenia in a limited patient population. ■



# Patient Management System a Success

Early detection is the key to safe management of CLOZARIL®-induced agranulocytosis. Clinicians are expressing approval of the new Clozaril Patient Management System<sup>SM</sup> (CPMS<sup>SM</sup>), a comprehensive system of WBC testing, pharmacy, clinical laboratory and drug distribution services, all linked to compliance with required safety monitoring. The program has been tested in pilot studies across the U.S. and has achieved over 99% blood monitoring compliance on the part of the patients — without interfering with the physician's medical control.

The system is designed to detect falling WBC counts that may be indicative of impending agranulocytosis. In the event of abnormal test results, the physician will be notified immediately. If the abnormal test shows only a downward trend from a normal WBC count to a count that has not yet reached leukopenia, additional blood work, such as a complete blood count and a differential count, should be performed. If the WBC count stabilizes, the patient returns to the normal cycle of weekly monitoring.

*Patients who are discontinued from CLOZARIL (clozapine) because of severe leukopenia or agranulocytosis cannot resume therapy.* A single national database is maintained by CPMS in an effort to ensure that any patient who develops severe leukopenia or agranulocytosis is not rechallenged

with CLOZARIL (clozapine).

Caremark Homecare, Inc., a national home healthcare agency, has been chosen to implement the system. CPMS Case Administrators arrange for patients' blood to be drawn weekly, and the samples sent for analysis to Roche Biomedical Laboratories, a national clinical laboratory. A Clozapak<sup>TM</sup> seven-day supply of CLOZARIL (clozapine) is released upon collection of blood samples. CPMS operates on the principle of "No blood, no drug" to ensure that CLOZARIL (clozapine) is administered in the safest possible manner. The drug will be obtainable only through the Clozaril Patient Management System.

A CPMS Case Administrator coordinates WBC testing, reporting and drug delivery. For inpatients, weekly monitoring is performed in the hospital. Case Administrators arrange for weekly monitoring of outpatients. If a WBC test is missed, the Case Administrator will reschedule collection and pickup to transport the blood specimen to the laboratory.

When the patient's blood sample is collected, a week's supply of CLOZARIL (clozapine) is dispensed (see chart). Each week, results of the WBC count are sent to the prescribing psychiatrist. The Case Administrator will alert the psychiatrist immediately by telephone if the white blood cell count drops significantly.

In addition to its safety benefits, CPMS can also enhance clinical care, according to Richard Wagner, MD. Dr. Wagner is director of the Rhode Island Psychiatric Research and Training Center, one of 16 sites selected for the U.S. multicenter CLOZARIL comparative study. He said that the weekly patient follow-up provided by CPMS often improves compliance with the drug regimen and decreases recidivism. Some patients chronically hospitalized will respond so dramatically they can be discharged.

Clinicians who would like more information about CPMS may contact their Sandoz Mental Health Sales Representative. ■

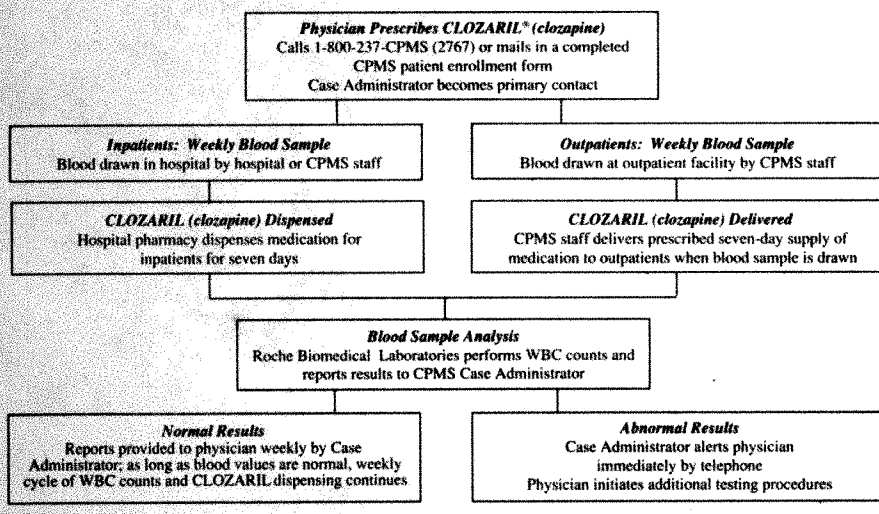
## Management System Frees Psychiatrists From Routine Tasks

The Clozaril Patient Management System<sup>SM</sup> (CPMS<sup>SM</sup>) relieves psychiatrists of the burden of hematological monitoring that must accompany CLOZARIL® therapy. The mandatory weekly white blood cell counts are conducted by Caremark Homecare, Inc., a national home healthcare agency, under the supervision of an agency Case Administrator, who arranges for the specimens to be transported and analyzed by Roche Biomedical Laboratories, a national clinical laboratory.

The physician need only call 1-800-237-CPMS (2767) to prescribe CLOZARIL (clozapine) or mail in a completed CPMS patient enrollment form. Thereafter, the Case Administrator will coordinate blood testing and drug dispensing, and report blood test results to the prescribing psychiatrist. At all times, the physician retains clinical control of the patient.

When the patient's WBC count is normal, the drug will be dispensed routinely, with the report mailed to the psychiatrist. Should a drop in WBC count occur, the psychiatrist will be contacted immediately by telephone. ■

### How the Clozaril Patient Management System<sup>SM</sup> (CPMS<sup>SM</sup>) Works



## Investigators Report Virtual Absence of Certain Acute EPS

Unlike standard antipsychotics, a virtual absence of certain acute extrapyramidal side effects (EPS), such as acute dystonia, is associated with CLOZARIL® administration. The incidence of other EPS, such as akathisia and rigidity, is also much lower with CLOZARIL therapy than with other agents. In a double-blind comparison of CLOZARIL (clozapine) and chlorpromazine/benztrapine, 11 of 76 chlorpromazine-treated patients discontinued therapy because of poorly tolerated EPS. In contrast, only one of 75 CLOZARIL patients stopped treatment because of EPS. There have been no confirmed cases of tardive dyskinesia in over 15 years' worldwide experience with clozapine. ■

## Side Effects Profile (Continued from page 3)

study, the mean and median doses were both approximately 600 mg/day. Patients must be advised not to engage in any activity where sudden loss of consciousness could cause serious risk to themselves or others, e.g., the operation of complex machinery, driving an automobile, swimming, climbing, etc.

Particular attention should be paid to patients with underlying cardiovascular disease or arrhythmias. Sustained tachycardia is a frequent occurrence in patients (25%) taking CLOZARIL tablets, with patients having an average increase in pulse rate of 10-15 bpm. Hypotension (9%) and hypertension (4%) are other cardiovascular effects associated with CLOZARIL (clozapine). ■

Please see brief summary of prescribing information on following page.



# CLOZARIL

(clozapine)  
TABLETS

**CAUTION:** Federal law prohibits dispensing without a prescription.

## CONTRAINDICATIONS

CLOZARIL is contraindicated in patients with myeloproliferative disorders, or a history of CLOZARIL-induced agranulocytosis or severe granulocytopenia. CLOZARIL should not be used simultaneously with other agents having a well-known potential to suppress bone marrow function. As with more typical antipsychotic drugs, CLOZARIL is contraindicated in severe central nervous system depression or comatose states from any cause.

## WARNINGS

### General

BECAUSE OF THE SIGNIFICANT RISK OF AGRANULOCYTOSIS, A POTENTIALLY LIFE-THREATENING ADVERSE EVENT (SEE BELOW), CLOZARIL SHOULD BE RESERVED FOR USE IN THE TREATMENT OF SEVERELY ILL SCHIZOPHRENIC PATIENTS WHO FAIL TO SHOW AN ACCEPTABLE RESPONSE TO ADEQUATE COURSES OF STANDARD ANTIPSYCHOTIC DRUG TREATMENT, EITHER BECAUSE OF INSUFFICIENT EFFECTIVENESS OR THE INABILITY TO ACHIEVE AN EFFECTIVE DOSE DUE TO INTOLERABLE ADVERSE EFFECTS FROM THOSE DRUGS. CONSEQUENTLY, BEFORE INITIATING TREATMENT WITH CLOZARIL, IT IS STRONGLY RECOMMENDED THAT A PATIENT BE GIVEN AT LEAST TWO TRIALS, EACH WITH A DIFFERENT STANDARD ANTIPSYCHOTIC DRUG PRODUCT, AT AN ADEQUATE DOSE AND FOR AN ADEQUATE DURATION.

PATIENTS WHO ARE BEING TREATED WITH CLOZARIL MUST HAVE A BASELINE WHITE BLOOD CELL (WBC) AND DIFFERENTIAL COUNT BEFORE INITIATION OF TREATMENT, AND A WBC COUNT EVERY WEEK THROUGHOUT TREATMENT, AND FOR FOUR WEEKS AFTER THE DISCONTINUATION OF CLOZARIL.

CLOZARIL IS AVAILABLE ONLY THROUGH THE CLOZARIL PATIENT MANAGEMENT SYSTEM<sup>SM</sup> (CPMS<sup>SM</sup>).

### Agranulocytosis

Agranulocytosis, defined as a granulocyte count (polys + bands) of less than 500 per mm<sup>3</sup>, has been estimated to occur in association with CLOZARIL use at a cumulative incidence at one year of approximately 1.3%, based on the occurrence of 15 U.S. cases out of 1743 patients exposed to CLOZARIL during its clinical testing prior to domestic marketing. All of these cases occurred at a time when the need for close monitoring of WBC counts was already recognized. This reaction could prove fatal if not detected early and therapy interrupted. While no fatalities have been associated with the U.S. agranulocytosis cases, and all cases have recovered fully, the U.S. sample is too small to reliably estimate the case fatality rate. Of the 112 cases of agranulocytosis reported worldwide in association with CLOZARIL use as of December 31, 1986, 35% were fatal. However, few of these deaths occurred since 1977, at which time the knowledge of CLOZARIL-induced agranulocytosis became more widespread, and close monitoring of WBC counts more widely practiced. Nevertheless, it is unknown at present what the case fatality rate will be for CLOZARIL-induced agranulocytosis, despite strict adherence to the recommendation for weekly monitoring of WBC counts.

Treatment should not be initiated if the WBC count is less than 3500 per mm<sup>3</sup>, or if the patient has a history of a myeloproliferative disorder, or previous CLOZARIL-induced agranulocytosis or granulocytopenia. Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat or any other signs of infection. If, after the initiation of treatment, the total WBC count has dropped below 3500 per mm<sup>3</sup> or it has dropped by a substantial amount from baseline, even if the count is above 3500 per mm<sup>3</sup>, or if immature forms are present, a repeat WBC count and a differential count should be done. If subsequent WBC counts and the differential count reveal a total WBC count between 3000 and 3500 per mm<sup>3</sup> and a granulocyte count above 1500 per mm<sup>3</sup>, twice weekly WBC counts and differential counts should be performed.

If the total WBC count falls below 3000 per mm<sup>3</sup> or the granulocyte count below 1500 per mm<sup>3</sup>, CLOZARIL therapy should be interrupted and patients should be carefully monitored for flu-like symptoms or other symptoms suggestive of infection. CLOZARIL therapy may be resumed if no symptoms of infection develop, and if the total WBC count returns to levels above 3000 per mm<sup>3</sup> and the granulocyte count returns to levels above 1500 per mm<sup>3</sup>. However, in this event, twice-weekly WBC counts and differential counts should continue until total WBC counts return to levels above 3500 per mm<sup>3</sup>.

If the total WBC count falls below 2000 per mm<sup>3</sup> or the granulocyte count falls below 1000 per mm<sup>3</sup>, bone marrow aspiration should be considered to ascertain granulopoietic status. Protective isolation with close observation may be indicated if granulopoiesis is determined to be deficient. Should evidence of infection develop, the patient should have appropriate cultures performed and an appropriate antibiotic regimen instituted.

Patients whose total WBC counts fall below 2000 per mm<sup>3</sup>, or granulocyte counts below 1000 per mm<sup>3</sup> during CLOZARIL therapy should *not* be re-challenged with CLOZARIL. Patients discontinued from CLOZARIL therapy due to significant WBC suppression have been found to develop agranulocytosis upon re-challenge, often with a shorter latency on re-exposure. To reduce the chances of re-challenge occurring in patients who have experienced significant bone marrow suppression during CLOZARIL therapy, a single, national master file will be maintained confidentially within the CPMS (Clozaril Patient Management System).

Except for evidence of significant bone marrow suppression during initial CLOZARIL therapy, there are no established risk factors, based on worldwide experience, for the development of agranulocytosis in association with CLOZARIL use. However, a disproportionate number of the U.S. cases of agranulocytosis occurred in patients of Jewish background compared to the overall proportion of such patients exposed during the domestic development of CLOZARIL. Most of the U.S. cases occurred within 4-10 weeks of exposure, but neither dose nor duration is a reliable predictor of this problem. No patient characteristics have been clearly linked to the development of agranulocytosis in association with CLOZARIL use, but agranulocytosis associated with other antipsychotic drugs has been reported to occur with a greater frequency in women, the elderly and in patients who are cachectic or have serious underlying medical illness; such patients may also be at particular risk with CLOZARIL.

To reduce the risk of agranulocytosis developing undetected, CLOZARIL will be dispensed only within the Clozaril Patient Management System.

### Seizures

Seizure has been estimated to occur in association with CLOZARIL use at a cumulative incidence at one year of approximately 5%, based on the occurrence of one or more seizures in 61 of 1743 patients exposed to CLOZARIL during its clinical testing prior to domestic marketing (i.e., a crude rate of 3.5%). Dose appears to be an important predictor of seizure, with a greater likelihood of seizure at the higher CLOZARIL doses used.

Caution should be used in administering CLOZARIL to patients having a history of seizures or other predisposing factors. Because of the substantial risk of seizure associated with CLOZARIL use, patients should be advised not to engage in any activity where sudden loss of consciousness could cause serious risk to themselves or others, e.g., the operation of complex machinery, driving an automobile, swimming, climbing, etc.

### Adverse Cardiovascular Effects

Orthostatic hypotension can occur with CLOZARIL treatment, especially during initial titration in association with rapid dose escalation, and may represent a continuing risk in some patients. Tachycardia, which may be sustained, has also been observed in approximately 25% of patients taking CLOZARIL, with patients having an average increase in pulse rate of 10-15 bpm. The sustained tachycardia is not simply a reflex response to hypotension, and is present in all positions monitored. Either tachycardia or hypotension may pose a serious risk for an individual with compromised cardiovascular function. A minority of CLOZARIL-treated patients experience ECG repolarization changes similar to those seen with other antipsychotic drugs, including S-T segment depression and flattening or inversion of T waves, which all normalize after discontinuation of CLOZARIL. The clinical significance of these changes is unclear. However, in clinical trials with CLOZARIL, several patients experienced significant cardiac events, including ischemic changes, myocardial infarction, nonfatal arrhythmias and sudden unexplained death. Causality assessment was difficult in many of these cases because of serious preexisting cardiac disease and plausible alternative causes. Rare instances of sudden, unexplained death have been reported in psychiatric patients, with or without associated antipsychotic drug treatment, and the relationship of these events to antipsychotic drug use is unknown. CLOZARIL should be used with caution in patients with known cardiovascular disease, and the recommendation for gradual titration of dose should be carefully observed.

### Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). No cases of NMS have been attributed to CLOZARIL alone. However, there have been several reported cases of NMS in patients treated concomitantly with lithium or other CNS-active agents.

### Tardive Dyskinesia

A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of treatment, which patients are likely to develop the syndrome.

There are several reasons for predicting that CLOZARIL may be different from other antipsychotic drugs in its potential for inducing tardive dyskinesia, including the preclinical finding that it has a relatively weak dopamine blocking effect and the clinical finding of a virtual absence of certain acute extrapyramidal symptoms, e.g., dystonia. In addition, there have been no confirmed cases of tardive dyskinesia developing in association with CLOZARIL use. Nevertheless, it cannot yet be concluded, without more extended experience, that CLOZARIL is incapable of inducing this syndrome.

### PRECAUTIONS

Because of the significant risk of agranulocytosis and seizure, both of which present a continuing risk over time, the extended treatment of patients failing to show an acceptable level of clinical response should ordinarily be avoided. In addition, the need for continuing treatment in patients exhibiting beneficial clinical responses should be periodically re-evaluated. During CLOZARIL therapy, patients may experience transient temperature elevations above 100.4°F (38°C), with the peak incidence within the first three weeks of treatment. While this fever is generally benign and self-limiting, it may necessitate discontinuing patients from treatment. On occasion, there may be an associated increase or decrease in WBC count. Patients with fever should be carefully evaluated to rule out the possibility of an underlying infectious process or the development of agranulocytosis. In the presence of high fever, the possibility of neuroleptic malignant syndrome (NMS) must be considered. CLOZARIL has very potent anticholinergic effects, and great care should be exercised in using this drug in the presence of prostatic enlargement or narrow angle glaucoma. Because of initial sedation, CLOZARIL may impair mental and/or physical abilities, especially during the first few days of therapy. The recommendations for gradual dose escalation should be carefully adhered to, and patients cautioned about activities requiring alertness. Clinical experience with CLOZARIL in patients with concomitant systemic diseases is limited. Nevertheless, caution is advisable in using CLOZARIL in patients with hepatic, renal or cardiac disease.

### Information for Patients

Patients who are to receive CLOZARIL should be warned about the significant risk of developing agranulocytosis. They should be informed that weekly blood tests are required to monitor for the occurrence of agranulocytosis, and that CLOZARIL tablets will be made available only through a special program designed to ensure the required blood monitoring. Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat, malaise, mucous membrane ulceration or other possible signs of infection. Particular attention should be paid to any flu-like complaints or other symptoms that might suggest infection. Patients should be informed of the significant risk of seizure during CLOZARIL treatment, and they should be advised to avoid driving and any other potentially hazardous activity while taking CLOZARIL. Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration. Patients should notify their physician if they are taking, or plan to take, any prescription or over-the-counter drugs or alcohol. Patients should notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should not breast feed an infant if they are taking CLOZARIL.



**CLOZARIL<sup>®</sup>**

(clozapine)

TABLETS

**Drug Interactions**

The risks of using CLOZARIL in combination with other drugs have not been systematically evaluated. The mechanism of CLOZARIL-induced agranulocytosis is unknown; nonetheless, the possibility that causative factors may interact synergistically to increase the risk and/or severity of bone marrow suppression warrants consideration. Therefore, CLOZARIL should not be used with other agents having a well-known potential to suppress bone marrow function. Given the primary CNS effects of CLOZARIL, caution is advised in using it concomitantly with other CNS-active drugs. Because CLOZARIL is highly bound to serum protein, the administration of CLOZARIL to a patient taking another drug which is highly bound to protein (e.g., warfarin, digoxin) may cause an increase in plasma concentrations of these drugs, potentially resulting in adverse effects. Conversely, adverse effects may result from displacement of protein-bound CLOZARIL by other highly bound drugs.

CLOZARIL may also potentiate the hypotensive effects of antihypertensive drugs and the anticholinergic effects of atropine-type drugs. The administration of epinephrine should be avoided in the treatment of drug-induced hypotension because of a possible reverse epinephrine effect.

**Pregnancy Category B**

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, and in view of the desirability of keeping the administration of all drugs to a minimum during pregnancy, this drug should be used only if clearly needed.

**ADVERSE REACTIONS**

Adverse events observed in association with the use of CLOZARIL in clinical trials at an incidence of 5% or greater were: central nervous system complaints, including drowsiness/sedation, dizziness/vertigo, headache and tremor; autonomic nervous system complaints, including salivation, sweating, dry mouth and visual disturbances; cardiovascular findings, including tachycardia, hypotension and syncope; and gastrointestinal complaints, including constipation and nausea; and fever. Complaints of drowsiness/sedation tend to subside with continued therapy or dose reduction. Salivation may be profuse, especially during sleep, but may be diminished with dose reduction.

**DOSE AND ADMINISTRATION****Initial Treatment**

It is recommended that treatment with CLOZARIL begin at 25 mg once or twice daily, and then be continued with daily dosage increments of 25 to 50 mg/day, if well-tolerated, to achieve a target dose of 300 to 450 mg/day by the end of two weeks. Subsequent dosage increments should be made no more than once- or twice-weekly, in increments not to exceed 100 mg. Cautious titration and a divided dosage schedule are necessary to minimize the risks of hypotension, seizure, and sedation.

**Therapeutic Dose Adjustment**

Daily dosing should continue on a divided basis as an effective and tolerable dose level is sought. While many patients may respond adequately at doses between 300-600 mg/day, it may be necessary to raise the dose to the 600-900 mg/day range to obtain an acceptable response. [Note: In the multicenter study providing the primary support for the superiority of CLOZARIL in treatment resistant patients, the mean and median CLOZARIL doses were both approximately 600 mg/day.]

Because of the possibility of increased adverse reactions at higher doses, particularly seizures, patients should ordinarily be given adequate time to respond to a given dose level before escalation to a higher dose is contemplated.

Dosing should not exceed 900 mg/day.

**Discontinuation of Treatment**

In the event of planned termination of CLOZARIL therapy, gradual reduction in dose is recommended over a 1 to 2 week period. However, should a patient's medical condition require abrupt discontinuation (e.g., leukopenia), the patient should be carefully observed for the recurrence of psychotic symptoms.

CLOZARIL is available only through the Clozaril Patient Management System, a program that combines white blood cell testing, patient monitoring, pharmacy, and drug distribution services, all linked to compliance with required safety monitoring.

To prescribe CLOZARIL call 1-800-237-CPMS (2767) or mail in a completed CPMS Enrollment Form.

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**THE MANFRED S.  
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The American Psychiatric Association and the American Academy of Psychiatry and the Law invite applications for the 1991 Manfred S. Guttmacher Award.

This award is given for an outstanding contribution to the literature of forensic psychiatry in the form of a book, monograph, paper, or any other work presented at a professional meeting or published between May 1, 1989, and April 30, 1990. The award will be formally presented in May 1991 at the American Academy of Psychiatry and the Law meeting held in conjunction with the American Psychiatric Association Annual Meeting in New Orleans. The award includes an honorarium of \$500 and a plaque. The travel expenses of a nonmember winner will be reimbursed up to \$500. The recipient is expected to give an award lecture. The award will be cited in the Convocation of Fellows program of the 1991 APA Annual Meeting.

Anyone wishing to apply should submit six copies of work, along with six copies of an abstract to William H. Reid, M.D., M.P.H., Chairman, Guttmacher Award Board, American Psychiatric Association, 1400 K Street, N.W., Suite 327, Washington, DC 20005.

**Entries must be received by May 15, 1990. Entries will be acknowledged but not returned.**



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\*The 150-mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.

Please see brief summary of SINEQUAN® (doxepin HCl) prescribing information on next page.

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**References:** 1. Goldberg HL: Sleep disturbance as a manifestation of depression, in *Somatic Depression: Insights for Primary Care Physicians*. Proceedings of a symposium held in Miami, Dec 4, 1978. New York: Postgraduate Medicine Communications, pp 13-18. 2. Karacan I, Blackburn AB, Thornby JI, et al: The effect of doxepin HCl (Sinequan) on sleep patterns and clinical symptomatology of neurotic depressed patients with sleep disturbance, in *Sinequan® (doxepin HCl): A Monograph of Recent Clinical Studies*. Princeton, NJ: Excerpta Medica, 1977, pp 4-22. 3. Goldberg HL, Finnerty RJ: The use of doxepin in the treatment of symptoms of anxiety neurosis and accompanying depression: A collaborative controlled study. *Am J Psychiatry* 1972;129(July):74-77.

# SINEQUAN® (doxepin HCl)

## BRIEF SUMMARY

### SINEQUAN® (doxepin HCl) Capsules/Oral Concentrate

**Contraindications.** SINEQUAN is contraindicated in individuals who have shown hypersensitivity to the drug. Possibility of cross sensitivity with other dibenzoxepines should be kept in mind.

SINEQUAN is contraindicated in patients with glaucoma or a tendency to urinary retention. These disorders should be ruled out, particularly in older patients.

**Warnings.** The once-a-day dosage regimen of SINEQUAN in patients with intercurrent illness or patients taking other medications should be carefully adjusted. This is especially important in patients receiving other medications with anticholinergic effects.

**Usage in Geriatrics:** The use of SINEQUAN on a once-a-day dosage regimen in geriatric patients should be adjusted carefully based on the patient's condition.

**Usage in Pregnancy:** Reproduction studies have been performed in rats, rabbits, monkeys and dogs and there was no evidence of harm to the animal fetus. The relevance to humans is not known. Since there is no experience in pregnant women who have received this drug, safety in pregnancy has not been established. There has been a report of apnea and drowsiness occurring in a nursing infant whose mother was taking SINEQUAN.

**Usage in Children:** The use of SINEQUAN in children under 12 years of age is not recommended because safe conditions for its use have not been established.

## Drug Interactions.

**MAO Inhibitors:** Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least two weeks prior to the cautious initiation of therapy with SINEQUAN. The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

**Cimetidine:** Cimetidine has been reported to produce clinically significant fluctuations in steady-state serum concentrations of various tricyclic antidepressants. Serious anticholinergic symptoms (i.e., severe dry mouth, urinary retention and blurred vision) have been associated with elevations in the serum levels of tricyclic antidepressant when cimetidine therapy is initiated. Additionally, higher than expected tricyclic antidepressant levels have been observed when they are begun in patients already taking cimetidine. In patients who have been reported to be well controlled on tricyclic antidepressants receiving concurrent cimetidine therapy, discontinuation of cimetidine has been reported to decrease established steady-state serum tricyclic antidepressant levels and compromise their therapeutic effects.

**Alcohol:** It should be borne in mind that alcohol ingestion may increase the danger inherent in any intentional or unintentional SINEQUAN overdose. This is especially important in patients who may use alcohol excessively.

**Tolazamide:** A case of severe hypoglycemia has been reported in a type II diabetic patient maintained on tolazamide (1 gm/day) 11 days after the addition of doxepin (75 mg/day).

**Precautions.** Since drowsiness may occur with the use of this drug, patients should be warned of the possibility and cautioned against driving a car or operating dangerous machinery while taking the drug. Patients should also be cautioned that their response to alcohol may be potentiated.

Since suicide is an inherent risk in any depressed patient and may remain so until significant improvement has occurred, patients should be closely supervised during the early course of therapy. Prescriptions should be written for the smallest feasible amount.

Should increased symptoms of psychosis or shift to manic symptomatology occur, it may be necessary to reduce dosage or add a major tranquilizer to the dosage regimen.

**Adverse Reactions:** NOTE: Some of the adverse reactions noted below have not been specifically reported with SINEQUAN use. However, due to the close pharmacological similarities among the tricyclics, the reactions should be considered when prescribing SINEQUAN (doxepin HCl).

**Anticholinergic Effects:** Dry mouth, blurred vision, constipation, and urinary retention have been reported. If they do not subside with continued therapy, or become severe, it may be necessary to reduce the dosage.

**Central Nervous System Effects:** Drowsiness is the most commonly noticed side effect. This tends to disappear as therapy is continued. Other infrequently reported CNS side effects are confusion, disorientation, hallucinations, numbness, paresthesias, ataxia, extrapyramidal symptoms, seizures, tardive dyskinesia, and tremor.

**Cardiovascular:** Cardiovascular effects including hypotension, hypertension, and tachycardia have been reported occasionally.

**Allergic:** Skin rash, edema, photosensitization, and pruritus have occasionally occurred.

**Hematologic:** Eosinophilia has been reported in a few patients. There have been occasional reports of bone marrow depression manifesting as agranulocytosis, leukopenia, thrombocytopenia, and purpura.

**Gastrointestinal:** Nausea, vomiting, indigestion, taste disturbances, diarrhea, anorexia, and aphthous stomatitis have been reported. (See anticholinergic effects.)

**Endocrine:** Raised or lowered libido, testicular swelling, gynecomastia in males, enlargement of breasts and galactorrhea in the female, raising or lowering of blood sugar levels, and syndrome of inappropriate antidiuretic hormone secretion have been reported with tricyclic administration.

**Other:** Dizziness, tinnitus, weight gain, sweating, chills, fatigue, weakness, flushing, jaundice, alopecia, headache, exacerbation of asthma, and hyperpyrexia (in association with chlorpromazine) have been occasionally observed as adverse effects.

**Withdrawal Symptoms:** The possibility of development of withdrawal symptoms upon abrupt cessation of treatment after prolonged SINEQUAN administration should be borne in mind. These are not indicative of addiction and gradual withdrawal of medication should not cause these symptoms.

**Dosage and Administration.** For most patients with illness of mild to moderate severity, a starting daily dose of 75 mg is recommended. Dosage may subsequently be increased or decreased at appropriate intervals and according to individual response. The usual optimum dose range is 75 mg/day to 150 mg/day.

In more severely ill patients higher doses may be required with subsequent gradual increase to 300 mg/day if necessary. Additional therapeutic effect is rarely to be obtained by exceeding a dose of 300 mg/day.

In patients with very mild symptomatology or emotional symptoms accompanying organic disease, lower doses may suffice. Some of these patients have been controlled on doses as low as 25-50 mg/day.

The total daily dosage of SINEQUAN may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed the maximum recommended dose is 150 mg/day. This dose may be given at bedtime. **The 150 mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

Anti-anxiety effect is apparent before the antidepressant effect. Optimal antidepressant effect may not be evident for two to three weeks.

## Overdosage.

### A. Signs and Symptoms

1. Mild: Drowsiness, stupor, blurred vision, excessive dryness of mouth.
2. Severe: Respiratory depression, hypotension, coma, convulsions, cardiac arrhythmias and tachycardias.

Also: urinary retention (bladder atony), decreased gastrointestinal motility (paralytic ileus), hyperthermia (or hypothermia), hypertension, dilated pupils, hyperactive reflexes.

### B. Management and Treatment

1. Mild: Observation and supportive therapy is all that is usually necessary.
2. Severe: Medical management of severe SINEQUAN overdosage consists of aggressive supportive therapy. If the patient is conscious, gastric lavage, with appropriate precautions to prevent pulmonary aspiration, should be performed even though SINEQUAN is rapidly absorbed. The use of activated charcoal has been recommended, as has been continuous gastric lavage with saline for 24 hours or more. An adequate airway should be established in comatose patients and assisted ventilation used if necessary. EKG monitoring may be required for several days, since relapse after apparent recovery has been reported. Arrhythmias should be treated with the appropriate antiarrhythmic agent. It has been reported that many of the cardiovascular and CNS symptoms of tricyclic antidepressant poisoning in adults may be reversed by the slow intravenous administration of 1 mg to 3 mg of physostigmine salicylate. Because physostigmine is rapidly metabolized, the dosage should be repeated as required. Convulsions may respond to standard anticonvulsant therapy, however, barbiturates may potentiate any respiratory depression. Dialysis and forced diuresis generally are not of value in the management of overdosage due to high tissue and protein binding of SINEQUAN.

More detailed professional information available on request.

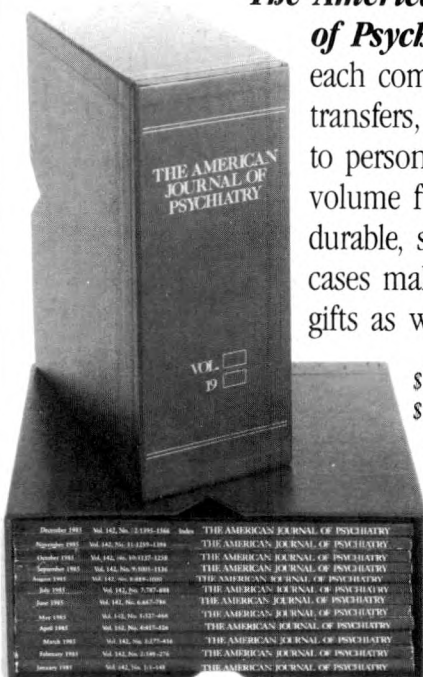
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A.M.A. 157:1274, 1955. Kovitz, B., et al.: A comparison of chlorpromazine and reserpine in chronic psychosis, *A.M.A. Arch. Neurol.* 55. Hunt, B.R., et al.: Chlorpromazine in the treatment of severe emotional disorders in children, *A.M.A. Am. J. Dis. Child.* 91:268, 1956. Winkelman, N.W., Jr.: Chlorpromazine in the treatment of porphyria, *J.A.M.A.* 162:174, 1956. Winkelman, N.W., Jr.: An appraisal of chlorpromazine, general principles for administration of chlorpromazine, based on experience with 1,090 patients, *Am. J. Psychiatry* 113:961, 1957. Langsley, D.G., et al.: A comparison of chlorpromazine and EST in treatment of acute schizophrenia and manic reactions, *A.M.A. Arch. Neurol. & Psychiatr.* 81:384, 1959. Ollendorff, R.H.V. Chlorpromazine therapy in acute and chronic schizophrenia, *Am. J. Psychiatry* 116:729, 1960. Winkelman, N.W., Jr.: A long-term investigation of constant and inconstant chlorpromazine administration over a period of six years with a discussion of the evolution of our therapeutic approach, *Psychiatry* 116:865, 1960. Remvig, J., et al.: Chlorprothixene (Truxal) compared to chlorpromazine, *Psychopharmacologia* (Berlin) 44:342-348, 1969. J. J., et al.: Drug treatment of schizophrenic patients, a comparative evaluation of chlorpromazine, chlorprothixene, fluphenazine, and triflupromazine, *Dis. Nerv. System* 23:698, 1962. Hollister, L.E., et al.: Comparison of intramuscular and oral administration of chlorpromazine, *Arch. Int. Pharmacodyn.* 144:571-578, 1963. Stabenau, J.R., et al.: A double-blind study of thioridazine and chlorpromazine; a study of recently hospitalized and acutely disturbed psychiatric patients, *Psychiatr. Q.* 38:42-61, 1964. Mays, J.E., Jr.: Acute intermittent porphyria in childhood, *J. Okla. State Med. Assoc.* 60:240-243, 1967. Lewis, S.A., et al.: Dose effects of chlorpromazine on human sleep, *Psychopharmacologia* (Berlin) 18:20-27, 1969. Clark, M.L., et al.: Chlorpromazine in chronic schizophrenia: behavioral dose response relationships, *Psychopharmacologia* (Berlin) 18:20-27, 1969. Leider, M.: Clinical pharmacology of chlorpromazine, *Vestn. Akad. Med. Nauk. SSSR* 26:84-86, 1971. Jovanovic, R., et al.: Effects of chlorpromazine and fluphenazine on some schizophrenic forms of behavior, *Br. J. Psychiatry* 120:223-224, 1972. Chacon, C., et al.: Clinical and work performance in phenothiazine therapy of schizophrenia: a comparative trial of fluphenazine decanoate, chlorpromazine and placebo, *Acta. Psychiatr. Scand.* 49:65-76, 1973. Klerman, G.L.: Drug therapy of schizophrenia. II. Current recommendations and future implications, *Drug Ther.* 3:28-32, 1973. Kolakowska, T., et al.: Clinical significance of plasma chlorpromazine levels. 2. Plasma levels of the drug, some of its metabolites and prolactin in patients receiving long term phenothiazine treatment, *Psychopharmacologia* (Berlin) 49:101-107, 1976. Rivera-Calimlim, et al.: Correlations of chlorpromazine and clinical response, *Community Psychopharmacol.* 2:215-222, 1978. Sikora, J., et al.: Chlorpromazine in the blood of schizophrenics, *Acta. Psychiatr. Scand.* 58:78-80, 1978. Bochkarev, V.K., et al.: Electroencephalographic profile and dynamics of individual EEG changes in patients with paranoid schizophrenia treated with aminazine (chlorpromazine): clinical electroencephalographic comparison, *Zh. Nevropatol. Psikhiatr.* 81:1192-1199, 1981. Dixon, P.A.F., et al.: Chlorpromazine metabolism and its significance in psychiatric patients, *J. Clin. Chem. Clin. Biochem.* (Br.) 19:653, (Abstract) 1981. Alfredsson, G., et al.: Relationships between drug concentrations in serum and CSF, clinical effects and monoamine oxidase activity in schizophrenic patients treated with sulpiride or chlorpromazine, *Acta. Psychiatr. Scand. Suppl.* 311:49-74, 1984. Aman, M.G., et al.: Conditioned stereotypic and stereotypic and conditioned behaviour of severely retarded patients; a pilot study, *J. Ment. Defic. Res.* 24:258-260, 1984. Harrydy, C., et al.: Effect of sulpiride in schizophrenic patients: a double-blind comparison with chlorpromazine, *Acta Psychiatr. Scand. Suppl.* 311:7-30, 1984. Black, J.L., et al.: Antipsychotic agents: a clinical comparison of haloperidol and chlorpromazine, *Encephale* 11:279, (Abstract) 1985. Faraone, S.V., et al.: Evolution of depressive and psychotic symptomatology in schizophrenia and treated with neuroleptics (controlled study haloperidol vs. chlorpromazine), *Encephale* 11:279, (Abstract) 1985.

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See complete prescribing information in SK&F literature or PDR. The following is a brief summary.

**Contraindications:** Comatose states or presence of large amounts of C.N.S. depressants.

**Warnings:** The possibility of extrapyramidal reactions from chlorpromazine may confuse the diagnosis of Reye's syndrome or other encephalopathy. Therefore, avoid use in children or adolescents with suspected Reye's syndrome.

May cause persistent tardive dyskinesia, which appears to be irreversible in some patients. Reserve chronic neuroleptic treatment for patients with chronic illness 1) that is known to respond to neuroleptics and 2) for whom there are no safer but equally effective treatment options. Use the smallest effective dose over the shortest treatment duration. If signs and symptoms of tardive dyskinesia develop, consider discontinuing the neuroleptic. A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. To manage NMS 1) discontinue immediately antipsychotic drugs and any other drugs not essential to concurrent therapy; 2) treat symptoms intensively and monitor; 3) where possible, treat serious concomitant medical problems. If antipsychotic treatment is needed after recovery from NMS, consider reintroducing drug therapy and monitor the patient carefully as recurrences of NMS have been reported. 'Thorazine' ampuls and vials contain sodium bisulfite and sodium sulfite; the sulfite may cause allergic reactions, including anaphylactic symptoms. In patients with bone marrow depression or previously demonstrated hypersensitivity (e.g., blood dyscrasias, jaundice) with phenothiazines, do not administer 'Thorazine' unless the potential treatment benefits outweigh the possible hazards. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery) especially during the first few days therapy. Avoid concomitant use with alcohol. May counteract antihypertensive effect of guanethidine and related compounds. Use in pregnancy only when essential. There are reported instances of prolonged jaundice, extrapyramidal signs, hyperreflexia or hyporeflexia in newborns whose mothers had received chlorpromazine. Chlorpromazine is excreted in the breast milk of nursing mothers.

**Precautions:** Advise patients and/or guardians of the risk of tardive dyskinesia from chronic therapy. Use cautiously in persons with cardiovascular, liver, renal or chronic respiratory disease, or with acute respiratory infections. Patients with a history of hepatic encephalopathy due to cirrhosis have increased sensitivity to the C.N.S. effects of chlorpromazine. Due to cough reflex suppression, aspiration of vomitus is possible. May prolong or intensify the action of C.N.S. depressants, organophosphorus insecticides, heat, atropine and related drugs. (Reduce dosage of concomitant C.N.S. depressants.) Anticonvulsant action of barbiturates is not intensified.

Neuroleptic drugs cause elevated prolactin levels that persist during chronic administration. Since approximately one third of human breast cancers are prolactin-dependent *in vitro*, this elevation is of potential importance if neuroleptic drug administration is contemplated in a patient with a previously detected breast cancer. Neither clinical nor epidemiologic studies to date, however, have shown an association between the chronic administration of neuroleptic drugs and mammary tumorigenesis. Chromosomal aberrations in spermatocytes and abnormal sperm have been demonstrated in rodents treated with certain neuroleptics. Use cautiously in glaucoma patients. May diminish the effect of oral anticoagulants, produce  $\alpha$ -adrenergic blockade, and lower the convulsive threshold; dosage adjustment of anticonvulsants may be required. May interfere with Dilantin® metabolism, causing 'Dilantin' toxicity. May cause false positive phenylketonuria test results. Do not use with Amipaque®†. Discontinue 'Thorazine' at least 48 hours before myelography, do not resume for at least 24 hours postprocedure, and do not use to control N/V prior to myelography or postprocedure with 'Amipaque'. Evaluate patients with a history of long-term therapy with 'Thorazine' and/or other neuroleptics periodically to decide whether the dosage could be reduced or therapy discontinued. Antiemetic effect may mask signs of overdosage of other drugs or obscure diagnosis and treatment of conditions such as intestinal obstruction, brain tumor and Reye's syndrome (see Warnings). When used concomitantly, may obscure vomiting as a sign of toxicity of a cancer chemotherapeutic agent. Discontinue high-dose, long-term therapy gradually. Patients with a history of long-term therapy with 'Thorazine' and/or other neuroleptics should be evaluated periodically for possible adjustment or discontinuance of drug therapy.

**Adverse Reactions:** Drowsiness; cholestatic jaundice; agranulocytosis, eosinophilia, leukopenia, hemolytic anemia, aplastic anemia, thrombocytopenic purpura and pancytopenia; postural hypotension, tachycardia, fainting, dizziness and occasionally a shock-like condition; reversal of epinephrine effects; EKG changes have been reported; neuromuscular (extrapyramidal) reactions: dystonias, motor restlessness, pseudo-parkinsonism, persistent tardive dyskinesia, psychotic symptoms, catatonik-like states, cerebral edema; convulsive seizures; abnormality of the cerebrospinal fluid proteins; urticarial reactions and photosensitivity, exfoliative dermatitis, contact dermatitis; asthma, laryngeal edema, angioneurotic edema, and anaphylactoid reactions; lactation and breast engorgement (in females on large doses), false positive pregnancy tests, amenorrhea, gynecomastia; hyperglycemia, hypoglycemia, glycosuria; dry mouth, nasal congestion, constipation, adynamic ileus, urinary retention, priapism, miosis, mydriasis; after prolonged substantial doses, skin pigmentation, epithelial keratopathy, lenticular and corneal deposits and pigmentary retinopathy, visual impairment; mild fever (after large I.M. doses); hyperpyrexia; increased appetite and weight; a systemic lupus erythematosus-like syndrome; peripheral edema.

NOTE: Sudden death in patients taking phenothiazines (apparently due to cardiac arrest or asphyxia due to failure of cough reflex) has been reported but no causal relationship has been established.

**How Supplied:** Tablets: 10 mg, 25 mg or 50 mg, in bottles of 100 and 1000; in Single Unit Packages of 100 (intended for institutional use only). For use in severe neuropsychiatric conditions, 100 mg and 200 mg, in bottles of 100 and 1000; in Single Unit Packages of 100 (intended for institutional use only).

**Spansule® brand of sustained release capsules:** 30 mg, 75 mg, 150 mg or 200 mg, in bottles of 50 and 500; in Single Unit Packages of 100 (intended for institutional use only). For use in severe neuropsychiatric conditions, 300 mg, in bottles of 50; in Single Unit Packages of 100 (intended for institutional use only).

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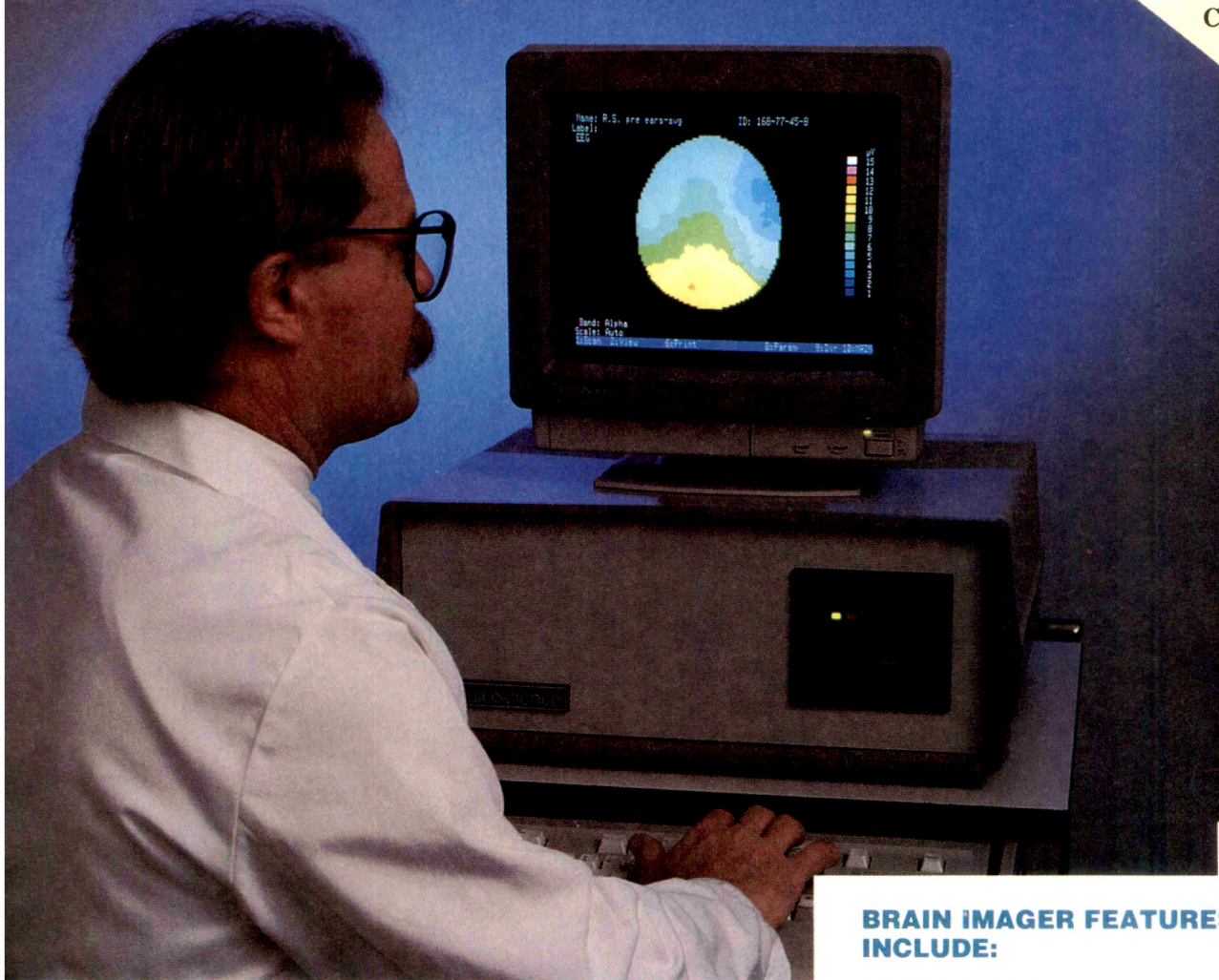


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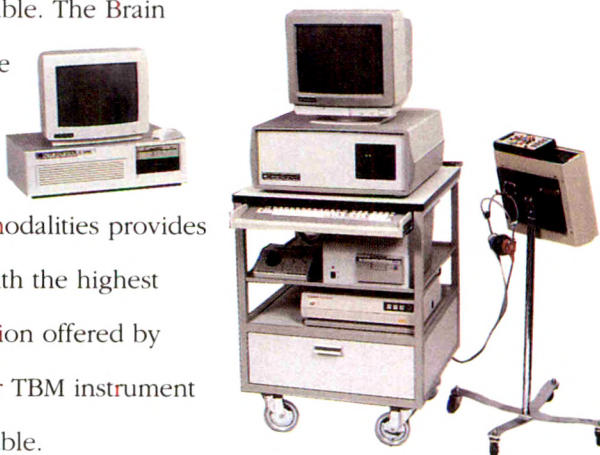
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- On Stress Disease and Evolution: A Unifying Theory**, by Graham William Boyd, M.B., B.S., M.D., Ph.D., F.R.A.C.P. Hobart, Australia, University of Tasmania, 1989, 229 pp., \$29.95 (paper).
- Master Clinicians on Treating the Regressed Patient**, edited by L. Bryce Boyer, M.D., and Peter L. Giovacchini, M.D. Northvale, N.J., Jason Aronson, 1990, 381 pp., \$50.00.
- La folie raisonnée**, edited by Michelle Cadoret. Paris, Presses Universitaires de France, 1989, 495 pp., no price listed (paper).
- PQR: Prescription for a Quality Relationship** (1988), by Allen Fay, M.D. New York, Fireside Books (Simon & Schuster), 1990, 227 pp., \$7.95 (paper).
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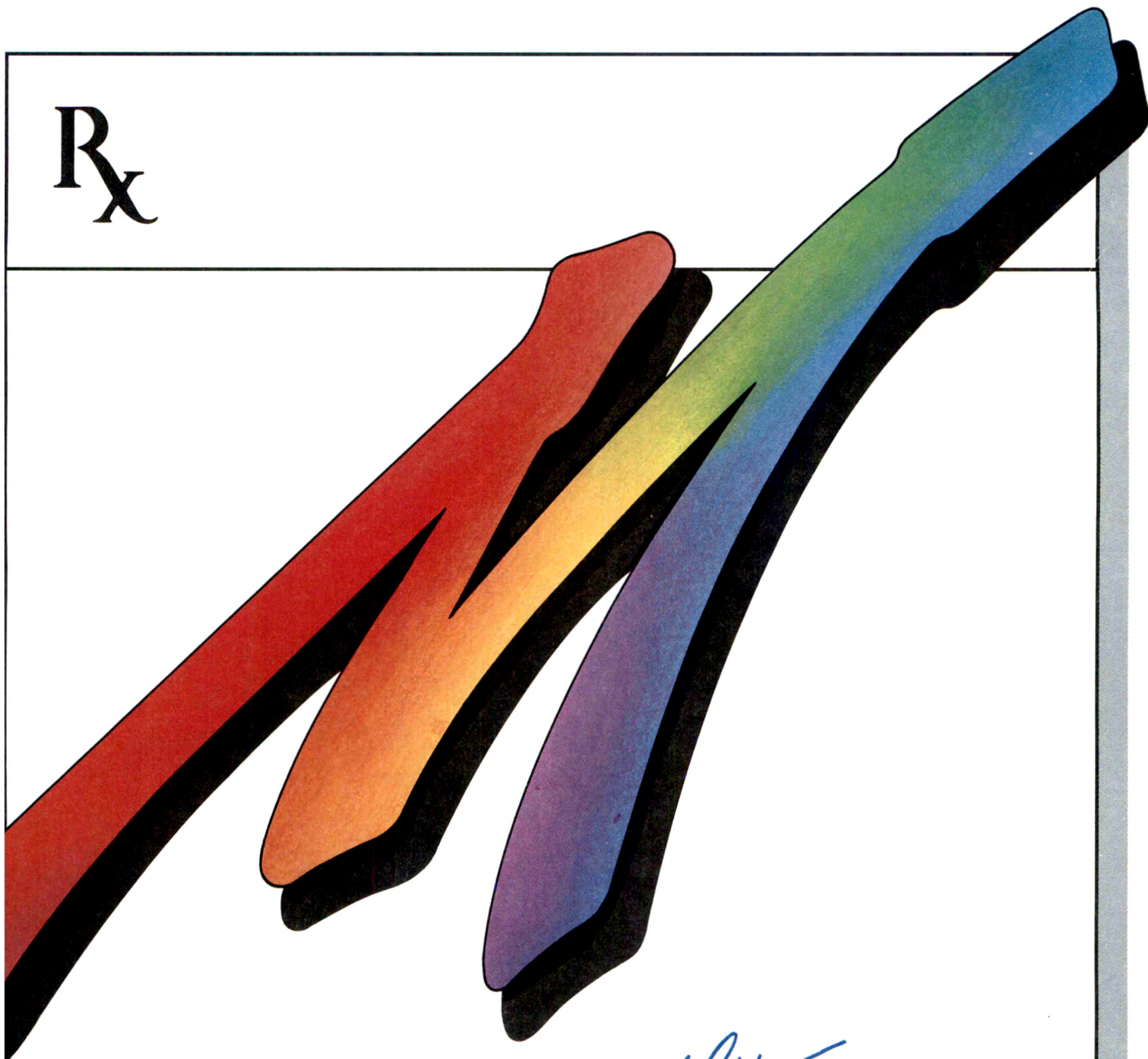
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## *Special Article*

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### Studies of the Epidemiology of Bulimia Nervosa

Christopher G. Fairburn, D.M., M.Phil., M.R.C.Psych., and Sarah J. Beglin, B.A.

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*Research on the epidemiology of bulimia nervosa has focused largely on the prevalence of the disorder. As methods have improved, consensus has increased regarding the prevalence rate among adolescent and young adult women—about 1%. However, the accuracy of this figure and its clinical significance must be questioned. In this synthesis of the epidemiological work to date, the authors review the literature from a clinical and research perspective. They recommend a shift in emphasis away from studies of the distribution of the disorder toward studies of the determinants of the whole spectrum of the disturbance that exists in the community.*

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**B**ulimia nervosa is an eating disorder that has three core features (1). First, there are recurrent episodes of overeating sometimes referred to as “binges”; second, there are various forms of behavior designed to control shape and weight, including extreme dieting, excessive exercising, self-induced vomiting, and the taking of laxatives or diuretics; and third, there are extreme concerns about shape and weight. The first articles on the disorder began to appear in the 1970s, and it was included in *DSM-III* under the name “bulimia.” Since then, the disorder has been the subject of much interest, stimulated, no doubt, by the large num-

ber of patients who have come forward seeking help for this hitherto little known problem (2, 3).

The topic that has perhaps attracted most research attention has been the epidemiology of the disorder. It is the aim of this paper to consider what has been learned from this large body of research. The majority of studies have been concerned with the prevalence of the disorder among adolescent and young adult women. These will be considered first, the studies being subdivided according to their method of case detection. Then, three special types of study will be considered: studies of subgroups thought to be either at high or low risk of developing bulimia nervosa, studies designed to investigate changes in prevalence over time, and studies with a longitudinal design.

#### PREVALENCE STUDIES

Most of the research on the epidemiology of bulimia nervosa has focused on its distribution; more than 50 prevalence studies have been conducted. The populations investigated have generally been those in which bulimia nervosa is thought to be most common, namely, Caucasian females between 14 and 40 years of age.

The studies may be usefully divided into three groups on the basis of their method of case detection. The first group consists of those that have relied exclusively upon subjects' responses to self-report questionnaires to make diagnoses of bulimia nervosa. The second and third groups have improved upon this practice by making diagnoses on the basis of clinical interviews, in most cases after the samples have been screened for potential cases through the use of a self-report questionnaire. With a two-stage design of this type, the accuracy of the prevalence rate obtained depends to a large extent upon the ability of the screening instrument to detect potential cases. An efficient instru-

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Received March 15, 1989; revision received July 12, 1989; accepted Aug. 24, 1989. From the Department of Psychiatry, Oxford University, Warneford Hospital. Address reprint requests to Dr. Fairburn, Department of Psychiatry, Oxford University, Warneford Hospital, Oxford OX3 7JX, England.

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**TABLE 1. Prevalence of Key Features of Bulimia Nervosa Determined by Studies Using Self-Report Questionnaires**

Feature	Prevalence (%)			Number of Studies
	Mean	SD	Range	
Binge eating				
Current	35.8	21.4	7-79	16
At least weekly	15.7	9.4	5-39	11
Current strict dieting or fasting	29.0	15.0	7-55	8
Self-induced vomiting				
Current	8.0	5.1	2-21	14
At least weekly	2.4	1.4	0-4	8
Laxative misuse				
Current	5.8	3.3	2-12	11
At least weekly	2.7	1.6	1-5	5

ment should detect all cases while minimizing the number of false positive subjects who need to be interviewed. In the second group of studies the diagnoses were made by interview, but the performance of the screening instrument was not formally evaluated. The findings of these studies must be distinguished from those of the third group, in which either there was an evaluation of the screening instrument or there was no screening phase at all and instead the entire sample was interviewed.

#### *Studies That Relied Upon Self-Report Questionnaires*

The majority of the studies of the prevalence of bulimia nervosa have based their diagnoses exclusively on subjects' responses to self-report questionnaires (4-41). In these studies the subjects completed questionnaires designed to elicit the core features of bulimia nervosa. On the basis of their responses, the prevalence rates of individual features of the disorder, as well as the prevalence of the full syndrome itself, have been calculated.

Table 1 shows the prevalence rates of the key features of bulimia nervosa, as determined by these studies. It can be seen that binge eating, the ill-defined but widely used term to denote the cardinal feature of bulimia nervosa, is a commonly reported behavior. On average, across the 16 studies that provide the necessary information, more than one-third of the respondents report current episodes of binge eating; however, the range in the figures obtained is considerable. Of the behavior used to control shape or weight, strict dieting or fasting is the most prevalent, being reported by more than one-quarter of respondents. Current self-induced vomiting and laxative misuse are much less common, especially when practiced weekly. Few of the studies attempted to identify the attitudinal disturbance characteristic of bulimia nervosa (1), described by Russell (42) as a "morbid fear of becoming fat" and in *DSM-III-R* as a "persistent overconcern with shape or weight." (This feature was not included in the *DSM-III* criteria.) Indeed, since so few studies have attempted to assess the presence of these attitudes, and

their methods have been so varied, no conclusions can be drawn regarding the prevalence of these attitudes. The same applies to the use of diuretics, appetite suppressants, and exercise as means of controlling shape and weight.

Table 2 presents the figures for the prevalence of bulimia nervosa itself. The mean prevalence across the self-report studies of the *DSM-III* syndrome of bulimia is almost 10%. Since the *DSM-III* criteria have been criticized for being overinclusive (1), many investigators have added severity criteria with the hope of increasing the similarity between cases detected in community surveys and those seen in clinics. This has resulted in markedly lower prevalence rates being obtained. For example, if it is specified that binge eating should occur at least weekly, the average prevalence of *DSM-III* bulimia decreases markedly, and if it is required that purging should also occur at this rate, the mean prevalence falls still further. Four studies have determined the prevalence of the syndrome bulimia nervosa, employing either Russell's original definition (42) or the *DSM-III-R* criteria. The latter are generally regarded as the most satisfactory criteria for diagnosis of the syndrome. Table 2 shows the mean prevalence rates and the ranges across these studies.

There are three reasons to have misgivings about the findings and interpretation of these prevalence studies. The first concerns the samples themselves. Half of them have consisted of college students, often those enrolled in psychology classes at prestigious private universities. This group could hardly be considered representative of the group of women in the community thought to be vulnerable to bulimia nervosa. The findings of the early media-based surveys suggest that students form only a minority of those with the disorder (43, 44). Other populations that have been studied include subjects who attend family planning clinics (7, 28) and general practices (9, 35); however, as with students, there is difficulty generalizing from them to women in the general population. For example, subjects who have a significantly low weight are likely to be underrepresented in family planning clinics, since their sexual appetite may be low or even absent, whereas women with bulimia nervosa may be overrepresented among general practice patients because of the psychological and physical problems that usually accompany the disorder.

The second problem concerns the response rates obtained. Often these have been unsatisfactory, the mean  $\pm$  SD response rate across the studies being  $74.4\% \pm 20.9\%$ , and ranging from 34% to 100%. Clearly, in studies with a low response rate there is a definite possibility of bias, since the respondents may not be representative of the sample from which they were drawn: People with bulimia nervosa may be more or less likely than others to return self-report questionnaires about eating habits and attitudes. In some studies the problem of response rate has been overcome by studying "captive" populations such as subjects who attend clinics. With populations of this type, a response rate

TABLE 2. Prevalence of Bulimia Nervosa Determined by Studies That Used Three Methods of Case Detection

Diagnosis	Self-Report Questionnaires				Interview—Preliminary Studies				Interview—More Sophisticated Studies			
	Prevalence (%)			Number of Studies	Prevalence (%)			Number of Studies	Prevalence (%)			Number of Studies
	Mean	SD	Range		Mean	SD	Range		Mean	SD	Range	
DSM-III bulimia	9.0	4.3	3–19	20	1.9	1.9	0–5	4	1.5	1.0	1–3	4
DSM-III bulimia with weekly binge eating	3.6	2.0	0–7	13	—	—	—	0	—	—	—	—
DSM-III bulimia with weekly binge eating and purging	2.8	2.8	1–10	11	—	—	—	0	1.0	—	—	1
Bulimia nervosa diagnosed with Russell (42) or DSM-III-R criteria	2.6	1.0	2–4	4	1.6	—	—	1	0.9	0.3	0–1	4

of over 90% can often be obtained. For example, the two studies of subjects who attended family planning clinics (7, 28) had response rates of 96% and 89%, respectively. However, the advantage of studying captive populations is offset by the difficulty, already mentioned, of generalizing from them to women in the general population.

The most major shortcoming shared by these studies is their method of case detection. They have relied exclusively upon self-report questionnaires to identify the key features of bulimia nervosa and thereby to make diagnoses. This procedure is not satisfactory, since several of the central features of the disorder present major difficulties of definition and interpretation (45). A good example is binge eating. Most of the questionnaires ask about binge eating, yet this term does not have a generally accepted specific meaning. It certainly cannot be assumed that people who report eating in binges, however defined, necessarily experience eating episodes of the type seen among patients with bulimia nervosa. This is probably one of the reasons why the range in the figures obtained for binge eating is so wide. Similar difficulties apply to the identification of the attitudes toward shape and weight that are characteristic of the disorder. For example, responses to questions in self-report questionnaires about "feeling fat" or "being preoccupied with your weight" are not a sufficient basis for deciding whether or not the subject has the overvalued ideas characteristic of people with bulimia nervosa. Instead, to elicit the key features of bulimia nervosa and thereby make a diagnosis, it is generally accepted that a face-to-face clinical interview is required. The inclusion of a clinical diagnostic interview in more recent studies therefore represents a significant methodological advance.

#### *Preliminary Interview-Based Studies*

There are five studies in this group (46–50). They have in common the fact that a two-stage design was used in which a self-report screening instrument was employed to identify individuals with probable bulimia nervosa; these individuals were then interviewed to establish a definite diagnosis. Unfortunately, these

studies did not include a formal evaluation of the performance of their screening instrument. Therefore, their findings have to be interpreted with caution, since an uncertain number of cases may not have been interviewed and may thus have escaped detection. More confidence may be placed in the diagnoses themselves, however, since they were made by clinical interview. Regarding the two other methodological issues raised earlier, satisfactory response rates were obtained in three of the five studies, but only one investigated a nonstudent group.

Table 2 summarizes the findings of these studies. It can be seen that the prevalence rates for both *DSM-III* bulimia and for bulimia nervosa are markedly lower than those from studies that used self-report questionnaires. These lower rates may well reflect the improved method for making diagnoses.

#### *More Sophisticated Interview-Based Studies*

The eight studies in this group are of two types. Six (51–56) used a two-stage design and included a test of the efficiency of their screening instrument. In the remaining two (57, 58), an attempt was made to interview the entire sample. While the latter approach must be the design of choice, since it obviates the need for a screening instrument, it is rarely practicable. Regrettably, both the studies that used this approach are flawed in other respects: In one the sample consisted of volunteers "obtained from local churches, industries, and university hospital clinics" (57), a group subject to a variety of selection biases, while in the other (58) the diagnostic interview consisted of a telephone call that lasted an average of 15 minutes—a procedure that few clinicians would regard as adequate to establish a diagnosis. With one possible exception, the six studies with a two-stage design are also open to serious criticism, since they share a significant methodological shortcoming. In the testing of the performance of the screening instrument, too few of those who scored below the chosen cutoff point were interviewed to determine the likely number of missed cases of bulimia nervosa. With a disorder with a prevalence in the region of 1% to 2%, several hundred of those who score



below the cutoff point should be interviewed to obtain a good idea of the false negative rate. In only one study was this number even approached (56). In the remainder, so few of those scoring below the cutoff point were interviewed that it would be surprising if any missed cases were detected. Thus, the reported sensitivities of these screening instruments are likely to be artificially inflated.

The studies in this group have included samples representative of those in the community thought to be prone to develop the disorder. Of particular note is the study by Johnson-Sabine et al. (56) of girls attending state schools in London. This study and those by King (52), Schotte and Stunkard (54), and Szmukler (51) also stand out for their high response rates. The importance of a high response rate is underscored by a subsidiary finding of the study by Johnson-Sabine et al. (56). They investigated nonrespondents and found that of a group of 17, two were receiving treatment for anorexia nervosa. These were the only cases of anorexia nervosa identified in the entire study. Whether some of the other nonrespondents had bulimia nervosa is not clear, but it is a possibility, given that the disorder is often deliberately hidden. This finding is not reassuring, since it suggests that eating disorders may be overrepresented among those who choose not to cooperate with prevalence studies; this conclusion is reinforced by King's finding (59) that all three women who refused to have a diagnostic interview had repeatedly consulted their family doctor with concerns about their weight.

In table 2 the findings of this group of studies are also summarized. The prevalence rates of bulimia nervosa were still lower than those from the preliminary interview-based studies. The consistency of the rates for bulimia nervosa, as defined either by Russell's criteria (42) or by those of *DSM-III-R*, is particularly striking. Thus, it seems that improved methodology has brought increasing consensus on the prevalence of the disorder. However, it is important not to confuse consistency with accuracy, a point that will be considered further in the Discussion section.

#### STUDIES OF SPECIAL SUBGROUPS

Rather than studying subjects from the general population, some studies have focused upon particular subgroups within society. Such studies are of potential interest, since, if the rates of bulimia nervosa obtained differ significantly from those in the general population, this may highlight factors that affect the risk of developing the disorder. Unfortunately, the studies of this type have been disappointing. Their methods have not been comparable to those of the more sophisticated prevalence studies, and none has set out to identify potential risk or protective factors. Nevertheless, some of their findings are of note.

#### Men

Many of the prevalence studies have included men in the samples studied, and their findings have confirmed the clinical impression that bulimia nervosa is uncommon among men. For example, King (52, 59), in one of the most rigorous studies to date, divided eating disorders of clinical severity into cases of bulimia nervosa and "partial syndrome," on the basis of a structured clinical interview. He found that the combined prevalence of these two categories of disorder was 3.9% among women and 0.5% among men. Given this finding and those of the other studies, it seems reasonable to conclude that the comparatively small number of men who present for the treatment of bulimia nervosa reflects a genuine difference in the prevalence of the disorder between the two sexes rather than being an artifact attributable to factors such as differential case detection and referral. None of the studies has examined the various possible explanations for this discrepancy between the sexes.

#### Nonwhites

Nonwhites are another group that has received particular attention. As with men, clinical experience suggests that bulimia nervosa is underrepresented among nonwhites, although a recent report suggests that the number of cases among blacks is increasing (60). One of the prevalence studies had a sufficient number of nonwhites among its sample to derive an estimate of the prevalence of bulimia nervosa among this subgroup (47), and there has been a single study of a black college population (61). In addition, ethnic differences in prevalence among schoolgirls in a town in the north of England have been investigated (62). With the exception of the last study, markedly lower rates of bulimia nervosa have been found among nonwhites than whites.

There has also been a comparison of Arab female students living in London with those living in Cairo (63). This study found a greater level of disturbance among the London students. Unfortunately, the findings of this study and, indeed, those of the other studies of nonwhites have been interpreted somewhat injudiciously. All the studies have relied upon self-report questionnaires to some extent, either to make diagnoses or as screening instruments, yet not one has evaluated their performance within the particular population being studied. It cannot be assumed that instruments of this type perform in the same way in different populations. This criticism applies to all the studies of special subgroups.

#### Athletes

Those who are under pressure to be physically fit have also been investigated. Clearly, athletes are a heterogeneous group with respect to the pressures that they face. While in almost every sport, build influences

performance, only in some is weight per se of critical importance. Two sports of particular interest are wrestling and horse racing. In both, the participants must repeatedly meet specific weight thresholds, and this may necessitate employing extreme weight-control measures. For example, both wrestlers (64) and jockeys (65) repeatedly dehydrate themselves to "make weight" or "waste," their terms for losing weight. Whether this puts them at risk of developing bulimia nervosa is not clear. The studies of wrestlers have not been designed to detect cases of bulimia nervosa, and that of jockeys was compromised by a low response rate. However, the jockey study (65) did obtain anecdotal accounts of trainee jockeys who had dropped out because of severe and uncontrolled weight loss; this was accompanied in one case by regular binge eating and vomiting. It seems possible that these trainees had indeed developed a clinical eating disorder.

Within populations in which weight is necessarily important, diagnosing eating disorders is often difficult, since many accepted diagnostic markers are open to misinterpretation. For example, as King (59) notes, it is essential to distinguish between behavior aimed at maintaining a particular weight for vocational or sporting reasons and that driven by the overvalued ideas characteristic of patients with eating disorders. Possibly a key factor to assess is the extent to which the individual's behavior remains under his or her control. If subjects report that they are no longer able to control their eating habits or attempts to lose weight, this suggests that they have developed a clinical eating disorder.

#### *People With Obesity*

Episodes of overeating are reported to be common among patients who are obese, and studies have shown that up to 40% of these patients meet the criteria for the *DSM-III* syndrome of bulimia (66). To our knowledge, the proportion who meet the diagnostic criteria for bulimia nervosa has not been studied. It is likely to be considerably lower than 40%, since sustained strict dieting and regular purging are both uncommon among those who are overweight (67).

#### *People With Diabetes Mellitus*

Although the coincidence of eating disorders and diabetes was once thought to be uncommon (68), a succession of case reports describing the coexistence of the two disorders has been published over the past decade. There have also been a number of studies of the prevalence of eating disorders among patients with diabetes (69–73), although not one has been satisfactory. The samples investigated have mostly been unrepresentative of young diabetic patients as a whole, and the procedures used to detect cases have been fraught with problems. For example, investigators have tended to assume that screening instruments perform in the same or in a similar way with patients with

diabetes as they do with those who do not have the disease. This assumption is almost certainly not warranted, given that some degree of dietary restraint and concern about weight is encouraged among patients with diabetes.

#### *People With Psychiatric Disorders*

There have been three studies of the prevalence of bulimia nervosa among psychiatric inpatients. In common with the majority of other studies, their methods of case detection have had significant shortcomings. Their findings have also been inconsistent. One study found a very high prevalence (74); one found a prevalence equivalent to that of a college sample, although the rates of vomiting and laxative misuse were higher (75); and one found no cases at all (76).

To investigate the comorbidity of bulimia nervosa and other psychiatric disorders, inpatients are not a good group to study, since they are subject to a variety of selection biases. The ideal group would be a community sample of psychiatric cases, but to date there have been no studies of this group. There have been two small studies of the prevalence of eating disorders among patients receiving treatment for alcohol abuse (77, 78). In both, features suggestive of bulimia nervosa were found to be common. Whether this association would also be found among community samples of those who abuse alcohol is not known. It may be that the association is peculiar to a subgroup of those who drink excessively, perhaps those with associated personality disturbance.

#### STUDIES OF CHANGES IN PREVALENCE OVER TIME

Two studies have attempted to investigate changes in the prevalence of bulimia nervosa and its elements over time. In principle, if clear changes were identified, this might help identify factors of relevance to the etiology of the disorder. One of the studies was of schoolgirls (41), and the other was of college freshmen (22). Each involved studying a sample similar to one studied some years earlier. The study of schoolchildren found a decrease in the prevalence of binge eating and *DSM-III* bulimia (between 1981 and 1986), whereas the study of college freshmen found that the prevalence had increased (between 1980 and 1983). Since both studies relied exclusively upon self-report questionnaires to make diagnoses, not too much weight should be placed upon their findings.

#### LONGITUDINAL STUDIES

To evaluate the clinical significance of the findings of the prevalence studies it is important to know the extent to which community subjects with bulimia nervosa resemble those seen in clinics. Four preliminary longitudinal studies have been designed to address this



issue. The four longitudinal studies (39, 40, 59, 79) have yielded two findings of note. The first is that in many cases, eating disorder symptoms wax and wane in severity; this is especially true of subjects with less severe symptoms. The second is that there is a subgroup whose eating disorder appears to persist. This subgroup has the most severely disturbed eating habits and attitudes. Thus, it appears that community cases of bulimia nervosa may be heterogeneous with respect to course and that in only a minority does the eating disorder run a persistent course similar to that of clinical cases.

## DISCUSSION

It will be evident from this account of the epidemiological work to date that the goal of the majority of studies has been to determine the prevalence of bulimia nervosa among adolescent and young adult women. The studies have become increasingly sophisticated over the past decade, while at the same time, the diagnostic criteria for the disorder have been refined (80). These two influences have resulted in progressively lower estimates of the prevalence of the disorder. The most sophisticated studies are impressively consistent in finding that bulimia nervosa appears to have a prevalence rate of about 1% among adolescent and young adult women. However, as mentioned earlier, it is important not to confuse consistency with accuracy, since the studies may all be subject to equivalent sources of error. For example, the evidence that eating disorders are overrepresented among those who choose not to cooperate with prevalence studies suggests that the figures obtained may be an underestimate of the true rate. Whether it will ever be possible to obtain a precise figure for the prevalence of the disorder is open to doubt.

To evaluate the clinical significance of the findings of the prevalence studies, the degree of associated psychiatric and physical morbidity of community-based cases has to be known. When interpreting their findings, investigators have tended to assume that the clinical severity of these cases is equivalent to that of clinic-based cases. This assumption is not warranted, since there have been no studies in which the clinical characteristics of community-based and clinic-based cases have been compared, other than one investigation of the subgroup in the community who volunteer for treatment studies (81). Given the likely prevalence of bulimia nervosa, such a comparison of community-based and clinic-based cases would require screening a sizable population to identify a sufficient number of community-based cases. What is clear from the prevalence studies is that only a small subgroup of those with bulimia nervosa is actually in treatment. It is likely that this subgroup is atypical in a number of respects. For example, their eating habits may be more disturbed, and they may have greater levels of associated psychopathology. Until the psychiatric and physical morbid-

ity of community-based and clinic-based cases have been compared, it would seem reasonable to assume that the subjects detected in community surveys are a less disturbed group. Support for this assumption comes from the finding of the longitudinal studies that in only a minority of community-based cases does the eating disorder persist over time.

A problematic topic, yet one that has hardly been addressed, is the difficulty in applying accepted diagnostic criteria to subjects in the community (82). Existing criteria have been derived on the basis of the experience of clinicians who, of necessity, work with the small subgroup of individuals who seek treatment for an eating disorder. As already mentioned, this subgroup is likely to be atypical. In the community a spectrum of disturbance is encountered in which there appear to be no obvious discontinuities between normality and psychopathology. One major contribution that future epidemiological research could make would be to derive an empirically based classification of eating disorders that takes account of the full spectrum of disturbance that exists in the community. To do so, subjects representative of the whole spectrum would need to be assessed with a measure that is capable of generating both dimensional and categorical data (45, 83). In addition, subjects' psychiatric, physical, and social adjustment would need to be evaluated to determine the levels of eating disorder psychopathology that are associated with various degrees of impaired functioning. Preferably, such a study should be longitudinal in design, since, as Kendell has stated (84), "diagnostic concepts stand or fall by the strength of the prognostic and therapeutic implications they embody."

Research of this type would undoubtedly yield findings of both practical importance and theoretical interest. It would be of great value to know which forms of disturbance are likely to resolve of their own accord, since they would merit little or no therapeutic intervention; in contrast, those likely to persist would justify early detection and treatment. Knowledge of prognostic factors might also further our understanding of psychopathological mechanisms; for example, were the cognitive view of the maintenance of these disorders correct (85), the presence of extreme concerns about body shape and weight should be predictive of a poor outcome.

The ability of epidemiological studies to illuminate the etiology of disorders has yet to be exploited in this field. Of the epidemiological research conducted to date, the studies of special groups are potentially of greatest significance in this regard. To be informative, such studies need to start out with a hypothesis concerning putative etiological factors and a design capable of testing it. Regrettably, the few comparative studies thus far conducted have been concerned simply with the detection of possible differences in prevalence and not with their explanation.

An analytic research design that needs to be exploited is the case-control study. This type of study is

intended to test specific causal hypotheses. To obtain a sufficient number of representative cases, a large general population sample would first need to be screened. Then, the rates of occurrence of the individual factors under investigation could be compared in the cases and in suitably matched control subjects. If these rates were found to differ, this would suggest that the factors concerned may be of causal importance. "Cases" from across the whole spectrum of disturbance could be investigated in this way. Although complex to design and analyze, case-control studies are attractive, since several different causal hypotheses may be simultaneously tested.

## CONCLUSIONS

It has been our aim in this paper to evaluate the large body of research on the epidemiology of bulimia nervosa. It has emerged that as methods have improved, consensus has increased regarding the prevalence of the disorder among adolescent and young adult women. We question whether much is to be gained from further prevalence studies of the type conducted to date. Instead, comparisons of the characteristics of clinic- and community-based cases are needed to interpret the clinical significance of the prevalence rates obtained. In addition, it is our view that it is time for a shift in emphasis away from prevalence per se toward studies of the nature, course, and etiology of the full spectrum of disturbance that exists in the community. Research of this type should broaden and deepen our currently limited understanding of eating disorders.

## REFERENCES

1. Fairburn CG, Garner DM: The diagnosis of bulimia nervosa. *Int J Eating Disorders* 1986; 5:403-419
2. Fairburn CG, Cooper PJ, O'Connor M: Publicity and bulimia nervosa. *Br J Psychiatry* 1983; 142:101-102
3. Garner DM, Fairburn CG: Relationship between anorexia nervosa and bulimia nervosa: diagnostic implications, in *Diagnostic Issues in Anorexia Nervosa and Bulimia Nervosa*. Edited by Garner DM, Garfinkel PE. New York, Brunner/Mazel, 1988
4. Hawkins RC, Clement PF: Development and construct validation of a self-report measure of binge eating tendencies. *Addict Behav* 1980; 5:219-226
5. Halmi KA, Falk JR, Schwartz E: Binge-eating and vomiting: a survey of a college population. *Psychol Med* 1981; 11:697-706
6. Pyle RL, Mitchell JE, Eckert ED, et al: The incidence of bulimia in freshmen college students. *Int J Eating Disorders* 1983; 2: 75-85
7. Cooper PJ, Fairburn CG: Binge-eating and self-induced vomiting in the community: a preliminary study. *Br J Psychiatry* 1983; 142:139-144
8. Abraham SF, Mira M, Beumont PJV, et al: Eating behaviours among young women. *Med J Aust* 1983; 2:225-228
9. Zinkand H, Cadoret RJ, Widmer RB: Incidence and detection of bulimia in a family practice population. *J Fam Pract* 1984; 18:555-560
10. Moss RA, Jennings G, McFarland JH, et al: Binge eating, vomiting and weight fear in a female high school population. *J Fam Pract* 1984; 18:313-320
11. Katzman MA, Wolchik SA, Braver SL: The prevalence of frequent binge eating and bulimia in a non-clinical college sample. *Int J Eating Disorders* 1984; 3:53-61
12. Pope HG Jr, Hudson JL, Yurgelun-Todd D: Anorexia nervosa and bulimia among 300 suburban women shoppers. *Am J Psychiatry* 1984; 141:292-294
13. Pope HG, Hudson JL, Yurgelun-Todd D, et al: Prevalence of anorexia nervosa and bulimia in three student populations. *Int J Eating Disorders* 1984; 3:45-51
14. Johnson CL, Lewis C, Love S, et al: Incidence and correlates of bulimic behaviour in a female high school population. *J Youth Adolesc* 1984; 13:15-26
15. Carter JA, Duncan PA: Binge-eating and vomiting: a survey of a high school population. *Psychology in the Schools* 1984; 21: 198-203
16. Crowther JH, Post G, Zaynor L: The prevalence of bulimia and binge eating in adolescent girls. *Int J Eating Disorders* 1985; 4:29-42
17. Gray JJ, Ford K: The incidence of bulimia in a college sample. *Int J Eating Disorders* 1985; 4:201-210
18. Maceyko SJ, Nagelberg DB: The assessment of bulimia in high school students. *J Sch Health* 1985; 55:135-137
19. Touyz SW, Ivison DJ: The prevalence of bulimia in an Australian university sample, in *Eating Disorders: Prevalence and Treatment*. Edited by Touyz SW, Beumont PJV. Sydney, Williams & Wilkins/Adis, 1985
20. Healy K, Conroy RM, Walsh N: The prevalence of binge-eating and bulimia in 1063 college students. *J Psychiatr Res* 1985; 19:161-166
21. Hart KJ, Ollendick TH: Prevalence of bulimia in working and university women. *Am J Psychiatry* 1985; 142:851-854
22. Pyle RL, Halvorson PA, Neuman PA, et al: The increasing prevalence of bulimia in freshman college students. *Int J Eating Disorders* 1986; 5:631-647
23. Pertschuk M, Collins M, Kreisberg J, et al: Psychiatric symptoms associated with eating disorder in a college population. *Int J Eating Disorders* 1986; 5:563-568
24. Hendren RL, Barber JK, Sigafos A: Eating-disordered symptoms in a non-clinical population: a study of female adolescents in two private schools. *J Am Acad Child Psychiatry* 1986; 25: 836-840
25. Killen JD, Taylor CB, Telch MJ, et al: Self-induced vomiting and laxative and diuretic use among teenagers. *JAMA* 1986; 255:1447-1449
26. Zuckerman DM, Colby A, Ware NC, et al: The prevalence of bulimia among college students. *Am J Public Health* 1986; 76: 1135-1137
27. Herzog DB, Norman DK, Rigotti NA, et al: Frequency of bulimic behaviors and associated social maladjustment in female graduate students. *J Psychiatr Res* 1986; 20:355-361
28. Cooper PJ, Charnock D, Taylor MJ: The prevalence of bulimia nervosa: a replication study. *Br J Psychiatry* 1987; 151:684-686
29. Greenfield D, Quinlan DM, Harding P, et al: Eating behavior in an adolescent population. *Int J Eating Disorders* 1987; 6:99-111
30. Rosen JC, Gross J: Prevalence of weight reducing and weight gaining in adolescent girls and boys. *Health Psychol* 1987; 6: 131-147
31. Thelen MH, Mann LM, Pruitt J, et al: Bulimia: prevalence and component factors in college women. *J Psychosom Res* 1987; 31:73-78
32. Klesges RC, Mizes JS, Klesges LM: Self-help dieting strategies in college males and females. *Int J Eating Disorders* 1987; 6:409-417
33. Howat PM, Saxton AM: The incidence of bulimic behavior in a secondary and university school population. *J Youth Adolesc* 1988; 17:221-231
34. Mintz LB, Betz NE: Prevalence and correlates of eating disordered behaviors among undergraduate women. *J Counseling Psychol* 1988; 35:463-471
35. Ben-Tovim DI: *DSM-III*, draft *DSM-III-R*, and the diagnosis and prevalence of bulimia in Australia. *Am J Psychiatry* 1988; 145:1000-1002
36. Lachenmeyer JR, Muni-Brander P: Eating disorders in a non-



- clinical adolescent population: implications for treatment. *Adolescence* 1988; 23:303-312
37. Martin JR, Wollitzer AO: The prevalence, secrecy, and psychology of purging in a family practice setting. *Int J Eating Disorders* 1988; 7:515-519
38. Gross J, Rosen JC: Bulimia in adolescents: prevalence and psychosocial correlates. *Int J Eating Disorders* 1988; 7:51-61
39. Drenowski A, Yee DK, Krahn DD: Bulimia in college women: incidence and recovery rates. *Am J Psychiatry* 1988; 145:753-755
40. Striegel-Moore RH, Silberstein LR, Frensch P, et al: A prospective study of disordered eating among college students. *Int J Eating Disorders* 1989; 8:499-510
41. Johnson CL, Tobin DL, Lipkin J: Epidemiologic changes in bulimia behavior among female adolescents over a five year period. *Int J Eating Disorders* (in press)
42. Russell GFM: Bulimia nervosa: an ominous variant of anorexia nervosa. *Psychol Med* 1979; 9:429-448
43. Fairburn CG, Cooper PJ: Self-induced vomiting and bulimia nervosa: an undetected problem. *Br Med J* 1982; 284:1153-1155
44. Fairburn CG, Cooper PJ: Binge-eating, self-induced vomiting and laxative abuse: a community study. *Psychol Med* 1984; 14:401-410
45. Cooper Z, Fairburn CG: The Eating Disorder Examination: a semi-structured interview for the assessment of the specific psychopathology of eating disorders. *Int J Eating Disorders* 1987; 6:1-8
46. Nagelberg DB, Hale SL, Ware SL: The assessment of bulimic symptoms and personality correlates in female college students. *J Clin Psychol* 1984; 40:440-445
47. Nevo S: Bulimic symptoms: prevalence and ethnic differences among college women. *Int J Eating Disorders* 1985; 4:151-168
48. Meadows GN, Palmer RL, Newball EUM, et al: Eating attitudes and disorder in young women: a general practice based study. *Psychol Med* 1986; 16:351-357
49. Shefer T: "Abnormal" eating attitudes and behaviours among women students. *S Afr Med J* 1987; 72:419-421
50. Whitehouse AM, Button EJ: The prevalence of eating disorders in a UK college population: a reclassification of an earlier study. *Int J Eating Disorders* 1988; 7:393-397
51. Szmukler GI: Weight and food preoccupation in a population of English schoolgirls, in *Understanding Anorexia Nervosa and Bulimia*. Edited by Redfern DE. Columbus, Ohio, Ross Laboratories, 1983
52. King MB: Eating disorders in general practice. *Br Med J* 1986; 293:1412-1414
53. Williams RL, Schaefer CA, Shisslak CM, et al: Eating attitudes and behaviors in adolescent women: discrimination of normals, dieters, and suspected bulimics using the Eating Attitudes Test and Eating Disorder Inventory. *Int J Eating Disorders* 1986; 5:879-894
54. Schotte DE, Stunkard AJ: Bulimia vs bulimic behaviors on a college campus. *JAMA* 1987; 258:1213-1215
55. Freeman CPL, Henderson M: The BITE: indices of agreement. *Br J Psychiatry* 1988; 152:575-577
56. Johnson-Sabine E, Wood K, Patton G, et al: Abnormal eating attitudes in London schoolgirls—a prospective epidemiological study: factors associated with abnormal response on screening questionnaires. *Psychol Med* 1988; 18:615-622
57. Rand CSW, Kulda JM: Eating patterns in normal weight individuals: bulimia, restrained eating, and the night eating syndrome. *Int J Eating Disorders* 1986; 5:75-84
58. Drenowski A, Hopkins SA, Kessler RC: The prevalence of bulimia nervosa in the US college student population. *Am J Public Health* 1988; 78:1322-1325
59. King MB: Eating disorders in a general practice population: prevalence, characteristics and follow-up at 12 to 18 months. *Psychol Med Monogr Suppl* 1989; 14:1-34
60. Hsu LKG: Are the eating disorders becoming more common in blacks? *Int J Eating Disorders* 1987; 6:113-124
61. Gray JJ, Ford K, Kelly LM: The prevalence of bulimia in a black college population. *Int J Eating Disorders* 1987; 6:733-740
62. Mumford DB, Whitehouse AM: Increased prevalence of bulimia nervosa among Asian schoolgirls. *Br Med J* 1988; 297:718
63. Nasser M: Comparative study of the prevalence of abnormal eating attitudes among Arab female students of both London and Cairo universities. *Psychol Med* 1986; 16:621-625
64. Woods ER, Wilson CD, Masland RP: Weight control methods in high school wrestlers. *J Adolesc Health Care* 1988; 9:394-397
65. King MB, Mezey G: Eating behaviour of male racing jockeys. *Psychol Med* 1987; 17:249-253
66. Telch CF, Agras WS, Rossiter EM: Binge eating increases with increasing adiposity. *Int J Eating Disorders* 1988; 7:115-119
67. Marcus MD, Wing RR, Hopkins J: Obese binge-eaters: affect, cognitions and response to behavioral weight control. *J Consult Clin Psychol* 1988; 56:433-439
68. Crisp AH: The differential diagnosis of anorexia nervosa. *Proc R Soc Med* 1977; 70:685-690
69. Hudson JL, Wentworth SM, Hudson MS, et al: Prevalence of anorexia nervosa and bulimia among young diabetic women. *J Clin Psychiatry* 1985; 46:88-89
70. Rodin GM, Johnson LE, Garfinkel PE, et al: Eating disorders in female adolescents with insulin dependent diabetes mellitus. *Int J Psychiatry Med* 1986; 16:49-57
71. Rosmark B, Berne C, Holmgren S, et al: Eating disorders in patients with insulin-dependent diabetes mellitus. *J Clin Psychiatry* 1986; 47:547-550
72. Steel JM, Young RJ, Lloyd GG, et al: Clinically apparent eating disorders in young diabetic women: associations with painful neuropathy and other complications. *Br Med J* 1987; 294:859-862
73. Lloyd GG, Steel JM, Young RJ: Eating disorders and psychiatric morbidity in patients with diabetes mellitus. *Psychother Psychosom* 1987; 48:189-195
74. Kutcher SP, Whitehouse AM, Freeman CPL: "Hidden" eating disorders in Scottish psychiatric inpatients. *Am J Psychiatry* 1985; 142:1475-1478
75. Esman AH, Dechillo N, Moughan V: "Hidden" eating disorders in female patients (letter). *Am J Psychiatry* 1986; 143:803
76. Whitehouse AM, Adams R, Marche J: Are there hidden eating disorders among psychiatric inpatients? *Int J Eating Disorders* 1989; 8:235-238
77. Beary MD, Lacey JH, Merry J: Alcoholism and eating disorders in women of fertile age. *Br J Addict* 1986; 81:685-689
78. Lacey JH, Mourelis E: Bulimic alcoholics: some features of a clinical sub-group. *Br J Addict* 1986; 81:389-393
79. Yager J, Landsverk J, Edelstein CK: A 20-month follow-up study of 628 women with eating disorders, I: course and severity. *Am J Psychiatry* 1987; 144:1172-1177
80. Fairburn CG: The definition of bulimia nervosa: guidelines for clinicians and research workers. *Ann Behav Med* 1987; 9:3-7
81. Mitchell JE, Pyle RL, Eckert ED, et al: Patients versus symptomatic volunteers in bulimia nervosa research. *Int J Eating Disorders* 1988; 7:837-843
82. Szmukler GI: The epidemiology of anorexia nervosa and bulimia. *J Psychiatr Res* 1985; 19:143-153
83. Cooper Z, Cooper PJ, Fairburn CG: The validity of the Eating Disorder Examination and its subscales. *Br J Psychiatry* 1989; 154:807-812
84. Kendell RE: *The Role of Diagnosis in Psychiatry*. Oxford, Blackwell, 1975
85. Fairburn CG: The uncertain status of the cognitive approach to bulimia nervosa, in *The Psychobiology of Bulimia Nervosa*. Edited by Pirke KM, Vandereycken W, Ploog D. New York, Springer-Verlag, 1988

## The Psychiatric Patient's Right to Effective Treatment: Implications of *Osheroff v. Chestnut Lodge*

Gerald L. Klerman, M.D.

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*Although Osheroff v. Chestnut Lodge never reached final court adjudication, the case generated widespread discussion in psychiatric, legal, and lay circles. The author served as a consultant to Dr. Osheroff and testified that Chestnut Lodge failed to follow through with appropriate biological treatment for its own diagnosis of depression, focusing instead on Dr. Osheroff's presumed personality disorder diagnosis and treating him with intensive long-term individual psychotherapy. The author suggests that this case involves the proposed right of the patient to effective treatment and that treatments whose efficacy has been demonstrated have priority over treatments whose efficacy has not been established.*

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In recent decades, the courts have played a growing role in setting standards for psychiatric treatment. Important court decisions have established the patient's right to treatment, the patient's right to refuse treatment, and the patient's right to the least restrictive environment. Most of these court decisions have concerned patients in public institutions, many of whom have been hospitalized involuntarily under civil commitment statutes. With regard to nongovernmental institutions and the private practice of psychiatry, the courts have mainly been involved in cases of negligence, many of which involved adverse consequences

of biological treatments, such as drugs and convulsive therapy, or issues related to suicide (unpublished 1985 paper by K. Livingston).

Recently, the lawsuit of *Osheroff v. Chestnut Lodge* was settled out of court. The plaintiff claimed negligence because the institution failed to institute drug treatment and persisted in the use of individual psychotherapy as the sole treatment for his severe depression. This lawsuit is considered a landmark case dealing with a number of important issues confronting psychiatry—particularly the need for standards for psychiatric treatment and the ethical and legal consequences of the absence of such standards. The case has been widely discussed in legal journals (1), in the lay press (2), and in psychiatric circles (3-5); it was also discussed by Alan Stone in a paper given at the 1988 meeting of the American College of Psychiatrists.

The standards for psychiatric treatment include the safety, efficacy, and appropriateness of psychiatric treatment. These have long been subjects of controversy among the medical profession, psychiatry, and the public in general. The controversies have increased in recent years due to the introduction of new psychotropic drugs, new forms of psychotherapy and behavior therapy, increases in the types and numbers of mental health professionals, and the growing utilization of mental health services (6).

The lawsuit of *Osheroff v. Chestnut Lodge* raises a number of important clinical, scientific, public policy, and legal issues. The clinical issues have to do with the validity of psychiatric diagnoses and the criteria used in making treatment decisions. The scientific issues pertain to the nature of evidence for the safety and efficacy of psychiatric treatments. The public policy issues pertain to the respective roles and responsibilities of federal and state governments, the courts, and professional organizations in the protection of the welfare of patients with psychiatric conditions and the provision of careful, valid diagnoses and effective, hu-

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Received Nov. 15, 1988; accepted March 3, 1989. From the Department of Psychiatry, Cornell University Medical Center, New York. Address reprint requests to Dr. Klerman, New York Hospital, Cornell University Medical College, Payne Whitney Clinic, 525 East 68th St., New York, NY 10021.

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mane treatment and care. The legal issues have to do with the definition of standards of care in the criteria for malpractice and negligence.

I will summarize the salient clinical and legal developments in Dr. Osheroff's case, reviewing issues that have clinical, scientific, public policy, and legal implications. I will conclude with recommendations for clinical practitioners and for the profession.

#### THE CASE OF DR. OSHEROFF

Permission has been obtained from the patient to use his name and to report details of his history and treatment. Under usual circumstances, the patient's identity and that of the institutions where he was treated would not be given. However, since this case has already been discussed in the lay press (2) and in professional journals where the patient and the institutions have been frequently identified, further attempts at anonymity would be unjustified.

The patient, Dr. Rafael Osheroff, a 42-year-old, white male physician, was admitted to Chestnut Lodge in Maryland (in the Washington, D.C., metropolitan area) on Jan. 2, 1979. His history included brief periods of depressive and anxious symptoms as an adult; these had been treated on an outpatient basis. He had completed medical school and residency training, was certified as an internist, and became a subspecialist in nephrology. He was married and had three children—one with his current wife and two with his ex-wife.

Before his 1979 hospitalization, Dr. Osheroff had been suffering from anxious and depressive symptoms for approximately 2 years and had been treated as an outpatient with individual psychotherapy and tricyclic antidepressant medications. Dr. Nathan Kline, a prominent psychopharmacologist in New York, had initiated outpatient treatment with tricyclic medication, which, according to Dr. Kline's notes, produced moderate improvement. The patient, however, did not maintain the recommended dose, his clinical condition gradually worsened, and hospitalization was recommended.

The patient was hospitalized at Chestnut Lodge for approximately 7 months. During this time he was treated with individual psychotherapy four times a week. He lost 40 pounds, experienced severe insomnia, and had marked psychomotor agitation. His agitation, manifested by incessant pacing, was so extreme that his feet became swollen and blistered, requiring medical attention.

The patient's family became distressed by the length of the hospitalization and by his lack of improvement. They consulted a psychiatrist in the Washington, D.C., area, who spoke to the hospital leadership on the patient's behalf. In response, the staff at Chestnut Lodge held a clinical case conference to review the patient's treatment. They decided not to make any major changes—specifically, not to institute any medication regimen but to continue the intensive individual psy-

chotherapy. Dr. Osheroff's clinical condition continued to worsen. At the end of 7 months, his family had him discharged from Chestnut Lodge and admitted to Silver Hill Foundation in Connecticut.

On admission to Silver Hill Foundation, Dr. Osheroff was diagnosed as having a psychotic depressive reaction. His treating physician began treatment with a combination of phenothiazines and tricyclic antidepressants. Dr. Osheroff showed improvement within 3 weeks and was discharged from Silver Hill Foundation within 3 months. His final diagnosis was manic-depressive illness, depressed type.

Although the patient's final diagnosis on discharge from Silver Hill was manic-depressive illness, depressed type, testimony of the treating physician at Silver Hill revealed that, of the two *DSM-II* diagnoses that would subsume a depressive illness as severe as Dr. Osheroff's (manic-depressive illness, depressed type, and psychotic depressive reaction), the diagnosis of manic-depressive illness, depressed type, was selected because of the potential future complications regarding child custody that could arise from a diagnostic label including the term "psychotic." The Silver Hill physician further testified that she did not find evidence of a narcissistic personality disorder in Dr. Osheroff and that the correct diagnosis according to *DSM-III* terminology would be major depressive episode with psychotic features.

Following his discharge from Silver Hill Foundation in the summer of 1979, the patient resumed his medical practice. He has been in outpatient treatment, receiving psychotherapy and medication. He has not been hospitalized and has not experienced any episodes of depressive symptoms severe enough to interfere with his professional or social functioning. He has resumed contact with his children and has also become active socially.

#### THE LEGAL ACTIONS

In 1982, Dr. Osheroff initiated a lawsuit against Chestnut Lodge. He claimed that as a result of the negligence of Chestnut Lodge in not administering drug treatment, which would have quickly returned him to normal functioning, in the course of a year he lost a lucrative medical practice, his standing in the medical community, and custody of two of his children.

When Dr. Osheroff's suit came before the Maryland Health Care Arbitration Panel it was marked, among other things, by the large number of expert witnesses for the plaintiff, including Drs. Donald Klein, Bernard Carroll, Frank Ayd, and myself. The Arbitration Panel found for the plaintiff and awarded him financial damages (7). This was not a majority decision, however, and the director of the Arbitration Panel sent the panel back for an amended decision, which reduced the award. Under Maryland statute, once an arbitration process is concluded, any party to the proceedings may reject the panel's arbitration and call for court review.

Both sides appealed. The claimant, Dr. Osheroff, requested a jury trial, which was to have taken place in October 1987. However, before any action was taken by the court, a settlement was agreed on by both parties.

## CLINICAL AND SCIENTIFIC ISSUES

This case raises a number of clinical and scientific issues. The clinical issues have to do with the validity of the diagnosis and the process of decision making with regard to treatment. The scientific issues have to do with the nature of evidence for safety and efficacy of psychiatric treatments.

### *Divisions Within Psychiatry in the United States*

Resolution of both the clinical and scientific issues is made difficult by the divisions within psychiatry in the United States, where psychiatry is divided theoretically and clinically into different schools—biological, psychoanalytic, and behavioral (7). This aspect of the sociology of psychiatry and other mental health professions and its effect on training and practice have been documented for a number of years (8–11). Various terms have been used to describe these divisions and splits—schools, movements, ideologies, and paradigms, for example (10, 12, 13). Whatever term is used, there is agreement that the differences in theory and practice involve controversies over the nature of mental illness, the appropriateness of different forms of treatment, and the nature of the evidence for the safety and efficacy of such treatments.

Chestnut Lodge has played an important role in the modern history of psychiatry in the United States. For more than 40 years, Chestnut Lodge has been one of the major centers of theory and clinical practice in intensive individual psychotherapy based on psychoanalytic and interpersonal paradigms (14). Harry Stack Sullivan (15), who formulated the interpersonal theory of psychiatry, was a consultant to the institution. Many of his lectures and seminars at Chestnut Lodge have been published posthumously. Frieda Fromm-Reichmann was also on the staff at the same time. She had immigrated to the United States from Germany along with a large number of other leading psychoanalysts driven out of Europe by the Nazi regime. Fromm-Reichmann wrote a number of influential papers and books about the psychotherapeutic treatment of schizophrenia and manic-depressive illness (16, 17).

Several prominent U.S. psychiatrists were trained at Chestnut Lodge; many subsequently became leaders in clinical psychiatry. Alfred Stanton, who became psychiatrist-in-chief at McLean Hospital in Massachusetts, and Otto Will, who became medical director of the Austin Riggs Center in Massachusetts, are two notable examples. The writings of Sullivan (15), Fromm-Reichmann (16), Will (18), and others were influential

in many psychiatric residency training programs from 1950 through the 1970s.

In the 1950s and 1960s, new psychopharmacological agents and the findings of neuroscientific research began to influence psychiatric teaching, practice, and research. New forms of psychotherapy based on approaches other than psychoanalytic were applied. Professional controversies increased, particularly over the comparison of the therapeutic efficacy of the different forms of psychotherapy (psychoanalytic, behavioral, family, group) and over the relative efficacy and safety of the psychotherapies, used either alone or in combination with psychopharmacological agents (19).

### *Diagnostic Issues in Dr. Osheroff's Hospitalization*

At both Chestnut Lodge and Silver Hill Foundation there was agreement that Dr. Osheroff suffered from a severe depressive condition. There was disagreement, however, as to the diagnosis of narcissistic personality disorder. In a discussion of this case, Dr. Stone (3) described a "dispute" over the appropriate diagnosis: "The patient's psychiatric experts, in depositions that reflected their biological orientation, diagnosed him as having an obvious case of biological depression, emphasizing his vegetative disturbances. The private psychiatric hospital contended that the patient was properly diagnosed as having a narcissistic personality disorder."

It is to be noted that Dr. Osheroff's diagnoses at both Chestnut Lodge and Silver Hill Foundation were made in 1979 in accordance with *DSM-II*, APA's official nomenclature at the time of his hospitalization. *DSM-III*, which is the current diagnostic nomenclature for clinical psychiatric practice in the United States, did not come into use until 1980. *DSM-II* does not include a diagnostic category of narcissistic personality disorder, although that diagnostic category is included in *DSM-I* and in *DSM-III*.

*DSM-II* includes diagnostic categories of psychotic depressive reaction and manic-depressive illness, depressed type. Both refer to severe forms of depression. There is no evidence of clinical features of hypomania or mania in Dr. Osheroff's history or in the case records from either institution. The patient would not meet *DSM-III* criteria for bipolar disorder or *DSM-II* criteria for manic-depressive illness, manic or circular types.

The *DSM-II* diagnostic category of psychotic depressive reaction was replaced in *DSM-III* by major depressive episode with melancholia and/or major depressive episode with psychotic features. Melancholia is a term from the past denoting a particularly severe form of depression uniquely responsive to somatic drugs and/or ECT therapies. It is of note that the term "biological depression" does not appear in *DSM-II*, *DSM-III*, or *ICD-9*.

According to Chestnut Lodge records, there were differences in medical opinion as to the relative importance to be given to the patient's personality conflicts



and his depressive diagnosis as they influenced treatment decisions, not over the depressive diagnosis itself. As was the practice at that institution, the patient had two physicians, a psychiatrist-administrator and a psychotherapist (20). The hospital records suggest there may have been disagreement between these two physicians: the psychotherapist emphasized the need to treat the patient's personality problems as the major condition, and the administrator expressed concern over the continued severity of the patient's depressive symptoms and distressed behavior.

This aspect of the clinical process illustrates the tendency for many psychoanalytically oriented psychotherapists, both in institutional and in community practice, to focus treatment on a patient's personality conflict and character pathology rather than on symptoms. In *DSM-III* terms, there tends to be an emphasis on the axis II diagnosis and relatively less attention given to the axis I diagnosis. The axis I diagnosis, a severe depression in the case of Dr. Osheroff, is often missed, or, even if it is formulated, the personality disorder is chosen as the major target for treatment planning.

#### *The Disputed Diagnosis of Personality Disorder*

An important clinical consideration at issue in *Osheroff* is whether the patient suffered from a personality disorder as well as from depression and whether the presence of the narcissistic personality disorder militated against the use of medication for the depression. Long-term psychoanalytically oriented psychotherapy is often justified by the theory that some states of clinical depression derive from unresolved personality conflicts whose origins lie in developmental problems related to childhood intrafamilial psychopathology (17, 21). This theory of etiology and pathogenesis of depression is the subject of scientific research and professional discussion (22). Expert witnesses testified on this issue at the *Osheroff* hearings.

It should be noted that the psychiatric experts who testified in this case did not agree on the validity of the diagnosis of narcissistic personality disorder for the patient. One expert, a trained psychoanalyst who is currently responsible for Dr. Osheroff's treatment and who had treated him when the patient was 29 years old and at the time of his divorce (when he was 34 years old), did not accept the diagnosis of narcissistic personality disorder and testified to this effect at the court hearing. He noted the patient's successful life achievements before the onset of the illness episode that led to hospitalization at Chestnut Lodge, including his professional success as a nephrologist, his ability to sustain a high income, and his loving, empathic, and sensitive relationship with his children.

The admitting psychiatrist at Silver Hill Foundation did not make the diagnosis of any personality disorder. An expert witness called by Chestnut Lodge to testify at the court hearing also did not think that the patient had a narcissistic personality disorder. In contrast to

the near unanimity of expert opinion as to the patient's severe depressive condition, disagreement existed as to whether the patient met any criteria for narcissistic personality disorder.

#### *Scientific Evidence for Evaluating Psychiatric Treatment*

With regard to all kinds of therapeutics—pharmacotherapy, surgery, radiation, psychotherapy—the most scientifically valid evidence as to the safety and efficacy of a treatment comes from randomized controlled trials when these are available. Although there may be other methods of generating evidence, such as naturalistic and follow-up studies, the most convincing evidence comes from randomized controlled trials.

There have been many controlled clinical trials of psychiatric treatments; most have been conducted to evaluate psychopharmacological agents. These trials were initiated in the 1950s and 1960s in response to the controversy that followed the introduction of chlorpromazine, reserpine, and the other "tranquilizers." The application of controlled trials in psychopharmacology expanded after the passage in 1962 of the Kefauver-Harris Amendments to the Food, Drug, and Cosmetic Act, which mandated evidence of efficacy before a pharmaceutical compound could be approved by the Food and Drug Administration and marketed.

Research on the efficacy of psychotherapy has lagged behind that of psychopharmacology but has, nevertheless, been extensive. Smith et al. (23) analyzed more than 400 reports of psychotherapy research. Specific reviews of the evidence have appeared with regard to psychotherapy of neurosis (24), schizophrenia (25), depression (26), and obsessive-compulsive disorders (27).

In view of these developments, a review of the state of evidence regarding the treatments of the two psychiatric conditions diagnosed for Dr. Osheroff at the time of his hospitalization is in order.

With regard to the treatment of the patient's diagnosis of narcissistic personality disorder, there were no reports of controlled trials of any pharmacological or psychotherapeutic treatment for this condition at the time of his hospitalization (28). The doctors at Chestnut Lodge decided to treat Dr. Osheroff's personality disorder with intensive individual psychotherapy based on psychodynamic theory.

With regard to the treatment of the patient's *DSM-II* diagnosis of psychotic depressive reaction, there was very good evidence at the time of his hospitalization for the efficacy of two biological treatments—ECT and the combination of phenothiazines and tricyclic antidepressants. The combination pharmacotherapy was the treatment later prescribed at Silver Hill Foundation.

There are no reports of controlled trials supporting the claims for efficacy of psychoanalytically oriented intensive individual psychotherapy of the type advocated and practiced at Chestnut Lodge and administered to Dr. Osheroff. The closest approximation to a

controlled clinical trial of this form of intensive individual psychotherapy has been reported with hospitalized schizophrenic patients at two institutions in the Boston area (30). Contrary to the expectations of the investigators, one of whom was Dr. Alfred Stanton (who had held a senior position at Chestnut Lodge and was one of the authors of *The Mental Hospital* [20], which describes the Chestnut Lodge institution), the results indicated that intensive individual psychotherapy offered no advantage over standard treatment (hospitalization, medication, and supportive psychotherapy) for these patients.

McGlashan and Dingman (30, 31) have reported results from follow-up studies of groups of patients treated at Chestnut Lodge. The findings from this naturalistic study do not support the efficacy of long-term psychotherapy and hospitalization for severely depressed patients such as Dr. Osheroff.

It should not be concluded there is no evidence for the value of any psychotherapy in the treatment of depressive states. Depressive states are heterogeneous, and there are many forms of psychotherapy. There is very good evidence from controlled clinical trials for the value of a number of brief psychotherapies for nonpsychotic and nonbipolar forms of depression in ambulatory patients (26). The psychotherapies for which there is evidence include cognitive-behavioral therapy (32), interpersonal psychotherapy (14), and behavioral therapy (33). However, no clinical trials have been reported that support the claims for efficacy of psychoanalysis or intensive individual psychotherapy based on psychoanalytic theory for any form of depression.

#### *Personality Disorder and Depressed Patients' Response to Pharmacotherapy*

An important clinical issue raised by Osheroff has to do with the possible influence of a patient's diagnosis of personality disorder on the decision to use medication and on the expected response to medication of depressed patients treated either with medication alone or with medication in conjunction with psychotherapy.

Even if we assume that the personality disorder was correctly diagnosed in Dr. Osheroff's case, there is no evidence to support the premise that the presence of a narcissistic personality disorder militates against the use of antidepressant medication. Patients with a personality disorder in addition to depressive illness may be relatively less responsive to medication than those without an associated personality disorder (34). However, the presence of a personality disorder by itself does not contraindicate the prescription of appropriate medication or predict complete failure to respond.

A related therapeutic issue raised by the case has to do with the possible negative interactions between psychotherapy and pharmacotherapy for depression. Many psychoanalytically oriented psychotherapists have argued against the use of medication in patients receiving psychotherapy because of the possible adverse effects of the pharmacotherapy on the conduct of

the psychotherapy (35), although there is evidence that the combination of drugs and psychotherapy does not interfere with the psychotherapy of depression (36). Moreover, findings from controlled trials suggest that the combination of drugs and psychotherapy may have beneficial additive effects in the treatment of depression (37).

#### *Decision Making in Psychiatry*

Given this state of evidence, it is difficult to justify the rationale used by the Chestnut Lodge staff in forming their treatment plan and in making specific decisions. On the one hand, there was a body of scientific evidence from controlled trials attesting to the value of medication and/or ECT for the type of severe depression that the institution diagnosed this patient as having. On the other hand, there was no scientific evidence for the value of psychodynamically oriented intensive individual psychotherapy for either the patient's depressive condition or his diagnosis of personality disorder. Nevertheless, the patient was treated only with intensive psychotherapy.

It might have been reasonable to have undertaken a period of psychotherapy, particularly in view of the tendency of many depressive states to remit spontaneously. However, several clinical studies (38, 39) have concluded that, in the absence of intervention with somatic treatments, severe health impairment and greater mortality are associated with deep depressions.

The hospital continued its treatment plan for many months in the face of continued worsening of the patient's clinical state. Meanwhile, the prolonged hospitalization was having adverse effects on the patient's medical practice, financial resources, and marital and family relations.

#### PUBLIC POLICY ISSUES

In addition to clinical and scientific issues regarding diagnosis and treatment, this case raises some important issues regarding public policy. The policy issues have to do with the locus of responsibility for the protection and welfare of psychiatric patients and the activities of the government, the courts, and professional groups in establishing criteria for diagnosis and treatment.

#### *The Roles of the Federal and State Governments*

There is a federal agency, the Food and Drug Administration, that has statutory authority to review the evidence for the efficacy and safety of pharmacological treatments. Because of the Kefauver-Harris Amendments, a pharmaceutical firm that makes promotional claims for the efficacy of a drug is expected to present evidence from controlled trials in support of its assertions.



Consider, however, the situation with regard to psychotherapy. There are no statutory constraints on claims made for psychotherapy. No government body is authorized to review the evidence for psychotherapy or comment on its status. In the late 1970s, the Senate considered the creation of a National Commission on Mental Health Treatments, but the proposal was opposed by the mental health professions and was not enacted into law (40).

The National Institutes of Health (NIH) conduct consensus development conferences to review the evidence about specific procedures relevant to health and medicine, including the efficacy of treatments. An NIH consensus development conference was held on long-term drug treatments of affective disorders in 1984 (41), and a conference on electroconvulsive therapies was held in June 1985. However, the efficacy of psychotherapies has not been addressed by NIH.

It might be expected that two other federal government agencies concerned with health financing and disability—the Health Care Financing Administration and the Social Security Administration—would be involved in judgments as to the appropriateness of treatment, inasmuch as they are involved in the disbursement of large amounts of funds. The Health Care Financing Administration provides reimbursement under both Medicare and Medicaid, and the Social Security Administration determines the disability status of individuals with psychiatric illness. However, only limited efforts have been undertaken by these agencies to establish criteria for the safety and efficacy of treatments for which reimbursement will be provided. In this respect it is of note that the legislation establishing Medicaid and Medicare did not include criteria of safety or efficacy but, rather, discussed the criteria of reasonable and medical necessities. These criteria have not been explicated in specific regulations or procedures.

Although the federal government has no direct regulatory role with regard to psychotherapy, as it does with regard to drugs, it has a major role in supporting scientific research on mental illnesses and their treatment. The current imbalance in available evidence for efficacy of psychotherapy in relation to psychopharmacology has many sources; one is the social and economic structure of treatment research. In the case of pharmacological agents, the pharmaceutical industry is organized into large corporate bodies with considerable resources and incentives for research on the efficacy and safety of their products. In contrast, the psychotherapy “industry” is made up of many small firms and practitioners whose resources are less extensive and who are less capable of concerted action. It might be expected that the institutes of the Alcohol, Drug Abuse, and Mental Health Administration, particularly the National Institute of Mental Health (NIMH), would devote leadership and resources to treatment research, but here again, for complex reasons, NIMH’s record on funding psychotherapy re-

search is inadequate in total grants and not reflective of clinical practice or professional judgment. Efforts to correct this imbalance require greater cooperation between officials of the Alcohol, Drug Abuse, and Mental Health Administration and the professional leadership than has been achieved to date.

State governments have an important potential role with respect to these issues because licensure and certification of health professionals are the responsibility of state governments, as is the licensing of hospitals and clinics. Almost all state governments have established standards for professional licensing of physicians. An increasing number of state governments have established criteria for licensing and/or certification of psychotherapists, particularly psychologists and social workers. Similarly, almost all hospitals, including private psychiatric hospitals such as Chestnut Lodge and Silver Hill Foundation, require licensing in their respective states. However, no state has attempted to establish guidelines for the selection of treatments based on efficacy as part of licensing or certification requirements.

### *The Role of the Psychiatric Profession*

In the absence of a government body similar to the Food and Drug Administration, patients and the public might expect that professional associations such as APA, the American Psychological Association, or the National Association of Social Workers would undertake to provide this service to the public. No guidelines for treatment have emerged, however, although peer review criteria have been established. APA issued a report on the status of ECT in 1978 (42). The Royal Australian and New Zealand College of Physicians has contracted with the Australian Ministry of Social Security to undertake a quality assurance program, which has issued a series of reports reviewing the state of scientific evidence for selected diagnoses, including depression (43).

As of the late 1970s, when Dr. Osheroff was hospitalized, APA had published a manual for peer review of hospital utilization (44). With regard to the *DSM-II* diagnosis of psychotic depressive reaction, this manual recommended the use of drugs or ECT. It did not recommend individual psychotherapy. Furthermore, this manual recommended that if hospitalization has continued beyond 1 or 2 months, the case should be reviewed and the use of ECT or drug treatments considered. Therefore, although there were no government bodies offering legal guidelines, APA had established peer review criteria for the hospital treatment of psychotic depressive reaction (44).

APA is currently completing a project on psychiatric treatments under the leadership of T. Byram Karasu (45). Preliminary reports from this project have been published (46).

### *The Role of the Courts*

Given that there are no government bodies judging the efficacy of claims for psychotherapy, and given the limited efforts undertaken by professional associations, it is understandable that individual patients use the courts to seek redress for their grievances.

Governmental and professional bodies have been urged to issue judgments recommending treatments so that these criteria could be used by reimbursement agencies. In response, the Senate considered possible legislation to establish a National Commission on Mental Health Treatments in the late 1970s and, more recently, APA established the Commission on Psychiatric Therapies, led by Dr. Karasu. Some have advocated that the profession not make such recommendations in regard to treatment, assuming that if the profession did not take such actions the courts would ignore the issue or not take a position. The opposite seems to be the case. In the absence of professional criteria for standards of care, the courts are increasingly becoming the arena in which these disputes are adjudicated. Thus, case law and individual precedents may become the criteria for adequacy of diagnosis and treatment.

### *Biological Versus Psychodynamic Psychiatry*

Dr. Stone (3) raised the possibility that patients who have not improved after prolonged psychotherapeutic treatment may have found a way around their frustrations—a way provided by “biological psychiatrists.” Dr. Stone noted that biological psychiatry appears to be on the scientific ascendancy over psychodynamic psychiatry due to the prestige of the neurosciences and the evidence for efficacy of biological treatments.

My conclusion, however, is that the issue is not psychotherapy versus biological therapy but, rather, opinion versus evidence. The efficacy of drugs and other biological treatments is supported by a large body of controlled clinical trials. This body of evidence is all the more relevant to public policy in view of the paucity of studies indicating efficacy for individual psychotherapy.

It is regrettable that psychoanalysts and psychodynamic psychotherapists have not developed evidence in support of their claims for therapeutic efficacy. Twenty years ago, psychodynamic psychotherapy was the dominant paradigm of psychiatry in the United States, particularly in academic centers. A number of European psychiatrists, mostly psychoanalysts, contributed intellectual leadership and imaginative ideas to psychiatry here. Currently, however, psychoanalysis is on the scientific and professional defensive. This situation is, in part, a consequence of the failure of psychoanalysis to provide evidence for the efficacy of psychoanalysis and psychodynamic treatments for psychiatric disorders (47, 48).

In the period between World War I and World War II, biological psychiatry was in poor repute. Numerous

treatments, often of a heroic nature, were advocated: colonic resection, adrenalectomy, excision of teeth, lobotomy. These interventions were based on biological laboratory research of dubious quality and without any systematic studies of safety and efficacy. The situation changed after World War II, with evidence for the value of ECT for depression and insulin coma therapy for schizophrenia and, later, with the introduction of chlorpromazine and other drugs.

### *The Respectable Minority Doctrine*

The case of *Osheroff v. Chestnut Lodge* prompts a reevaluation of the doctrine of the respectable minority. Until recently, this doctrine held that if a minority of respected and qualified practitioners maintained a standard of care, this was an adequate defense against malpractice. I propose that this doctrine no longer holds if there is a body of evidence supporting the efficacy of a particular treatment and if there is agreement within the profession that this is the proper treatment of a given condition. Moreover, the respectable minority have a duty to inform the patient of the alternative treatments. In an unpublished 1985 paper discussing *Osheroff v. Chestnut Lodge*, K. Livingston wrote,

Under this view, the respectable minority view would still constitute a defense to a malpractice action where even 10% of practitioners would adhere to the treatment in question. However, the shield of the respectable minority rule would not be available unless the patient had been given informed consent after a disclosure of risk/benefits and alternatives to the therapy.

### *How Do We Proceed in the Absence of Consensus?*

When there is consensus in the profession as to the appropriate treatment for a given condition (in the case of *Osheroff*, the essential nature of biological treatment for severe depression), then a standard of care can be agreed on and can provide the basis for malpractice action.

However, how are we to evaluate claims for the efficacy of treatments for clinical conditions about which there is no consensus? What are the standards to be applied in diagnostic and clinical situations where there is no consensus within the field with regard to the treatment of the particular disorder? This is a serious policy question that, in the future, may become a legal question. In my opinion, there are three aspects to this issue: 1) What constitutes evidence for efficacy? 2) Who is responsible for generating the evidence? and 3) Who is to make the appropriate evaluation of treatments?

*What constitutes evidence of treatment?* In my view, the best available evidence as to efficacy comes from controlled trials. I am not taking the position that the only source of evidence for efficacy comes from such trials. Clinical experience, naturalistic studies, and fol-



low-up studies are also sources of relevant evidence. However, when results from controlled clinical trials are available, they should be given priority in any discussion of scientific evidence.

*Who should be responsible for generating the evidence?* What should be society's policy in regard to treatments for which there is no positive or negative evidence? This issue has not reached resolution, and I feel it merits further discussion within the profession.

My opinion is that the responsibility for generating evidence for efficacy rests with the individual, group, or organization that makes the claim for the safety and efficacy of a particular treatment. In the case of drugs, this responsibility is established by statute. If a pharmaceutical firm makes a claim for the efficacy of one of its products, it must generate enough evidence to satisfy the Food and Drug Administration before it can market the drug for prescription use.

No such mandate of responsibility exists for psychotherapy. Anyone can make a claim for the value of a form of psychotherapy—psychoanalysis, Gestalt, est, primal scream, etc.—with no evidence as to its efficacy.

What should be our position toward the claims of the efficacy in certain conditions of multiple treatments for which the evidence varies in quality and quantity? In my view, those treatments which make claims but have not generated evidence are in a weak position.

The efficacy of psychoanalysis and psychoanalytic treatments is in question for conditions for which there is evidence of efficacy with other treatments. For example, how many psychiatrists would justify long-term psychoanalytic treatment of panic disorder and/or agoraphobia when there is no evidence that this treatment works for these disorders but reasonably good evidence for the efficacy of certain drugs and/or forms of behavioral psychotherapy?

*Who is to evaluate the evidence?* A major problem arises as to the process by which the evidence regarding psychiatric treatments is to be evaluated. I believe there are serious deficiencies in our current professional and governmental arrangements for evaluating psychiatric treatments. In the case of drugs, we have the Food and Drug Administration, which makes such judgments according to established legal statutes and regulatory processes. There is no comparable statutory mandate for assessing the efficacy and safety of non-pharmacological treatments such as radiation, surgery, and psychotherapy.

In this situation, I believe the public has the right to expect that the medical profession will provide appropriate judgments as to the state of the evidence for treatments and establish criteria for standards of care. I maintain that the psychiatric profession has been lax in this responsibility and that the absence of professional consensus statements in our field leaves it open for the courts to be used by individuals, such as Dr. Osheroff, who feel they have been poorly treated and who believe they are entitled to redress of their grievances.

The fact that evidence changes is to my mind irrel-

evant to any policy or clinical discussion. The judgment on treatment of individual patients should be made according to the state of knowledge and professional practice at the time the individual patient is treated. In the case of Osheroff, this was 1979.

My strong preference would be for the profession to be more vigorous and more responsible in accepting this responsibility. I have stated these views on a number of occasions.

## RECOMMENDATIONS FOR THE PRACTICING CLINICIAN

What lessons can be learned from the case of *Osheroff v. Chestnut Lodge* that can be used by the practicing clinician, whether in institutional or community settings? As Dr. Stone pointed out in a paper given at the 1988 meeting of the American College of Psychiatrists, this case has no formal legal status because it was settled out of court. However, it has been widely discussed and will likely provide the basis for possible further legal actions in similar cases. In my opinion, this case goes a long way toward establishing the patient's right to effective treatment. The following recommendations are not intended to be legal standards for negligence or malpractice but, rather, to clarify professional responsibility.

1. The psychiatrist has a responsibility to make a comprehensive assessment, including determination of the proper diagnosis. The patient should be evaluated as to social and personal background, symptoms, and medical history, including personality, need for hospitalization, and possible suicidal risk. As part of this assessment, a diagnostic formulation should be made and, wherever possible, the formulation should be in accord with *DSM-III-R*. Of course, investigators and clinicians can and do depart from *DSM-III-R* categories and criteria whenever they have good scientific or professional reasons to do so (unpublished 1988 paper of Alan Stone). However, in my opinion, when this departure is done for an individual patient, in teaching, or in research, the psychiatrist should make explicit the departure from *DSM-III-R* and name the alternative diagnostic system used.

2. The psychiatrist has a responsibility to communicate to the patient the conclusions of the assessment, including a proper diagnosis. The patient has a right to be informed as to his or her diagnosis. Wherever possible, this should be communicated in a manner consistent with *DSM-III-R* terminology and criteria. I recognize that there is a legal as well as a professional dispute as to the nature of informed consent that is expected in different jurisdictions, but the fullest possible transmission of information will facilitate trust and integrity in the doctor-patient relationship (unpublished 1988 paper of Alan Stone).

3. The psychiatrist has a responsibility to provide information as to alternative treatments. The patient has the right to be informed as to the alternative treat-

ments available, their relative efficacy and safety, and the likely outcomes of these treatments. This is a special requirement on the respectable minority of physicians, since they should inform the patient that their treatment is not the one most widely held within the profession. In communicating these alternatives to the patient, the clinician should not make pejorative statements about former types of treatment. Statements such as "Drug treatment is only a crutch," "I don't believe in drug treatment," "ECT will cause brain damage," and "I don't believe in psychotherapy" are ill-advised and may be used by the patient against the clinician in subsequent complaints, including legal action.

4. The psychiatrist has a responsibility to use effective treatment. The patient has the right to the proper treatment. Proper treatment involves those treatments for which there is substantial evidence.

5. The psychiatrist has a responsibility to modify treatment plans or seek consultation if the patient does not improve. To quote K. Livingston (unpublished 1985 manuscript):

While psychiatry is not obliged to guarantee a cure, the courts may consider sympathetically arguments based upon the disparity between lengthy and costly treatment and the patient's failure to improve. Commentators note that when a patient fails to improve or deteriorates during treatment, there may be a duty upon the psychiatrist to abandon the treatment or to seek consultation.

Applied to the treatment of depression, the available evidence indicates that patients should begin to show improvement with medication within 4–8 weeks or with psychotherapy within 12–16 weeks. Failure of the patient to improve on a given treatment program within 3–4 months should prompt a reevaluation of the treatment plan, including consultation and consideration of alternative treatment.

## CONCLUSIONS

Dr. Stone (3) stated, "When it deals with psychiatry, the law must deal with a world of complexity, dubiety, and increasing conflict about efficacy." The availability of scientific evidence will increasingly be considered by the courts as relevant to such decisions. In large part this is because of the major advances in psychiatric therapeutic research. The availability of this growing body of evidence prompts new criteria for judging standards of care and treatment. In the presence of such evidence, practitioners and institutions who continue to rely on forms of treatment with limited efficacy will be on the defensive and at possible jeopardy for legal action.

Resolution of professional issues through the courts is far from ideal and has substantial social costs. Ideally, the profession is the best judge of the available evidence. The courts are a poor tribunal in which to resolve scientific and professional issues. However, in

the case of *Osheroff v. Chestnut Lodge*, there had been some professional agreement, as reflected in the APA peer review manual (44). The courts may be an appropriate arena for litigation when a small minority of the profession persist in practices that scientific evidence and professional judgment have deemed obsolete.

The problem of differences of opinion within a professional group has its analogy in issues of civil liberties—when should the majority insist that the minority accept its views? In the case of professional issues in psychiatry and medicine, however, the persistence of a minority dissent has implications beyond those of the profession because certain professional practices may involve harm to individual patients.

In the current situation in psychiatric practice, where there are large areas of ignorance, it behooves individual practitioners and institutions to avoid relying on single treatment approaches or theoretical paradigms. Thus, in modern psychiatry, treatment programs based only on psychotherapy or only on drugs are subject to criticism. Professionalism requires balancing available knowledge against clinical experience and promoting the advancement of scientific knowledge. In the case of treatment practices, such knowledge best comes from controlled trials.

## REFERENCES

1. Malcolm JG: Treatment choices and informed consent in psychiatry: implications of the Osheroff case for the profession. *J Psychiatry Law* 1986; 14:9–107
2. Sifford D: An improper diagnosis case that changed psychiatry. *Philadelphia Inquirer*, March 24, 1988, p 4E
3. Stone AA: The new paradox of psychiatric malpractice. *N Engl J Med* 1984; 311:1384–1387
4. Fink PJ: Response to the presidential address: is "biopsychosocial" the psychiatric shibboleth? *Am J Psychiatry* 1988; 145: 1061–1067
5. Campbell RJ III: Psychiatrists take law into own hands. *Psychiatr News*, April 1, 1988, p 4
6. Klerman GL: Trends in utilization of mental health services: perspectives for health services research. *Med Care* 1985; 23: 584–587
7. State of Maryland Health Claims Arbitration Board Amended Arbitration Panel Determination 82-262, Jan 18, 1984. Baltimore, Health Claims Arbitration Board, 1984
8. Hollingshead A, Redlich F: *Social Class and Mental Illness*. New York, John Wiley & Sons, 1958
9. Armor DJ, Klerman GL: Psychiatric treatment orientations and professional ideology. *J Health Soc Behav* 1968; 9:243–255
10. Strauss A, Schatzman L, Bucher R, et al (eds): *Psychiatric Ideologies and Institutions*. New York, Free Press, 1964
11. Havens L: *Approaches to the Mind*. Boston, Little, Brown, 1973
12. Kuhn TS: *The Structure of Scientific Revolutions*, 2nd ed: International Encyclopedia of Unified Science, vol 2, number 2. Chicago, University of Chicago Press, 1970
13. Klerman GL: The scope of depression, in *The Origins of Depression: Current Concepts and Approaches*. Edited by Angst J. New York, Springer-Verlag, 1983
14. Klerman GL, Weissman MM, Rounsaville BJ, et al: *Interpersonal Psychotherapy of Depression*. New York, Basic Books, 1984
15. Sullivan HS: *The Interpersonal Theory of Psychiatry*. New York, WW Norton, 1953
16. Fromm-Reichmann F: *Principles of Intensive Psychotherapy*. Chicago, Phoenix Books, 1960



17. Cohen MB, Baker G, Cohen R, et al: An intensive study of twelve cases of manic-depressive psychosis. *Psychiatry* 1954; 17:103-137
18. Will O: Schizophrenia: psychological treatment, in *Comprehensive Textbook of Psychiatry*, 3rd ed, vol 2. Edited by Kaplan HI, Freedman AM, Sadock BJ. Baltimore, Williams & Wilkins, 1980
19. Klerman GL: Drugs and psychotherapy, in *Handbook of Psychotherapy and Behavior Change: An Empirical Analysis*, 3rd ed. Edited by Garfield SL, Bergin AE. New York, John Wiley & Sons, 1986
20. Stanton AH, Schwartz MS: *The Mental Hospital*. New York, Basic Books, 1954
21. Arieti S, Bemporad J: *Severe and Mild Depression: The Psychotherapeutic Approach*. New York, Basic Books, 1978
22. Hirschfeld RMA, Klerman GL, Clayton PJ, et al: Assessing personality: effects of the depressive state on trait measurement. *Am J Psychiatry* 1983; 140:695-699
23. Smith ML, Glass GV, Miller TI: *The Benefits of Psychotherapy*. Baltimore, Johns Hopkins University Press, 1980
24. Andrews G, Harvey R: Does psychotherapy benefit neurotic patients? *Arch Gen Psychiatry* 1981; 38:1203-1208
25. Stanton AH, Gunderson JG, Knapp PH, et al: Effects of psychotherapy in schizophrenia, I: design and implementation of a controlled study. *Schizophr Bull* 1984; 10:520-563
26. Weissman MM, Jarrett RB, Rush AJ: Psychotherapy and its relevance to the pharmacotherapy of major depression, in *Psychopharmacology: The Third Generation of Progress*. Edited by Meltzer HY. New York, Raven Press, 1987
27. Marks I: Review of behavioral psychotherapy, I: obsessive-compulsive disorders. *Am J Psychiatry* 1981; 138:584-592
28. Griest JH, Jefferson JW, Spitzer RL: *Treatment of Mental Disorders*. New York, Oxford University Press, 1982
29. Klerman GL: Ideology and science in the individual psychotherapy of schizophrenia. *Schizophr Bull* 1984; 10:608-612
30. McGlashan TH: The Chestnut Lodge follow-up study, III: long-term outcome of borderline personalities. *Arch Gen Psychiatry* 1986; 43:20-30
31. Dingman CW, McGlashan TH: Discriminating characteristics of suicides: Chestnut Lodge follow-up sample including patients with affective disorder, schizophrenia and schizoaffective disorder. *Acta Psychiatr Scand* 1986; 74:91-97
32. Beck AT, Rush AJ, Shaw BF, et al: *Cognitive Therapy of Depression*. New York, Guilford Press, 1979
33. Lewinsohn PM: A behavioral approach to depression, in *The Psychology of Depression: Contemporary Theory and Research*. Edited by Friedman RJ, Katz MM. Washington, DC, VH Winston & Sons, 1974
34. Shea T, Glass DR, Pilkonis PA, et al: Frequency and implications of personality disorders in a sample of depressed outpatients. *J Personality Disorders* 1987; 1:27-42
35. Klerman GL: Psychotherapies and somatic therapies in affective disorders. *Psychiatr Clin North Am* 1983; 6:85-103
36. Rounsaville BJ, Klerman GL, Weissman MM: Do psychotherapy and pharmacotherapy for depression conflict? *Arch Gen Psychiatry* 1981; 38:24-29
37. Beitman BD, Klerman GL (eds): *Combining Psychotherapy and Drug Therapy in Clinical Practice*. Jamaica, NY, SP Medical & Scientific Books, 1984
38. Gottlieb JS, Huston PE: Treatment of schizophrenia: a comparison of three methods—brief psychotherapy, insulin coma, and electric shock. *J Nerv Ment Dis* 1951; 113:211-235
39. Avery D, Winokur G: Mortality in depressed patients treated with electroconvulsive therapy and antidepressant. *Arch Gen Psychiatry* 1976; 33:1029-1037
40. Klerman GL: The efficacy of psychotherapy as the basis for public policy. *Am Psychol* 1983; 38:929-934
41. Consensus Development Panel: NIMH/NIH Consensus Development Conference Statement: mood disorders: pharmacological prevention of recurrences. *Am J Psychiatry* 1985; 142:469-476
42. American Psychiatric Association Task Force Report 14: *Electroconvulsive Therapy*. Washington, DC, APA, 1978
43. Andrews G: A treatment outline for depressive disorders. *Aust NZ J Psychiatry* 1983; 17:129-146
44. American Psychiatric Association Peer Review Committee: *Manual of Psychiatric Peer Review*. Washington, DC, APA, 1976
45. American Psychiatric Association Commission on Psychotherapies: *Psychotherapy Research: Methodological and Efficacy Issues*. Washington, DC, APA, 1982
46. American Psychiatric Association Commission on Psychiatric Therapies: *The Psychiatric Therapies*. Washington, DC, APA, 1984
47. Grunbaum A: *The Foundations of Psychoanalysis: A Philosophical Critique*. Berkeley, University of California Press, 1984
48. Klerman GL: The scientific tasks confronting psychoanalysis: a review of Grunbaum's *Foundations of Psychoanalysis*. *Behavioral and Brain Sciences* 1986; 9:245

# Law, Science, and Psychiatric Malpractice: A Response to Klerman's Indictment of Psychoanalytic Psychiatry

Alan A. Stone, M.D.

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*The Osheroff litigation, which is central to Klerman's paper, ended in an out-of-court settlement. The author states that there is no legal precedent for the so-called right to effective treatment and that the case history was a much more complicated clinical scenario than Klerman reports. He concludes that there is neither in the law nor in the clinical facts a sound or certain basis for Klerman's conclusions or for the sweeping policy reforms and standardized clinical procedures he urges. Although they are directed against traditional psychoanalytic psychiatrists, Klerman's proposals could have serious consequences for the innovation, diversity, and independent thought essential to scientific progress in psychiatry.*

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It is the potential legal implications of Klerman's conclusions that will be most noteworthy to his colleagues, insurance companies, and the lawyers for whom these matters are relevant. It is therefore necessary for me to set out here what I think is the potential legal import of Klerman's paper, recognizing that he can claim I have misunderstood what he intended merely as clinical recommendations. The problem is that clinical recommendations made by one of the leading authorities in psychiatry carry legal weight in court as standards of care. This point will be amplified in what follows. I also assume that what Klerman says in his paper he is prepared to say in court or in depositions, just as he did in the *Osheroff* litigation. The principal inquiry to be considered here, therefore, is how Klerman's paper would be understood by a lawyer contemplating a malpractice suit against a psychoanalytically oriented psychiatrist.

As Klerman et al. (1) have written elsewhere, this is the age of depression; the treatment of depression, therefore, is the principal task of clinical psychiatry. The significance of Klerman's recommendations, implicit in his paper, is that it is clinically improper and

therefore negligent to provide exclusively psychoanalytic treatment or psychoanalytically based psychotherapy for any patient with any depressive disorder. It is also reasonable to conclude that Klerman recommends that the provision of such exclusive treatments should be deemed improper for any other *DSM-III-R* disorder for which there is an alternative treatment that has any demonstrated efficacy in a clinical trial.

The reader might suppose that such exclusive treatments are not negligent, in Klerman's view, if the patients have been appropriately informed of the more efficacious treatment alternatives and have been told that the kind of treatment being proposed has no "scientifically" proven efficacy. Patients could choose exclusive psychoanalytic treatment in this scenario, despite being appropriately informed about the "scientific" evidence. The law of informed consent might then insulate the psychiatrist from liability. However, Klerman's paradigm of professional responsibility is aimed at regulating the exclusive practice of personal psychiatry. It includes as its fourth responsibility that of providing treatments for which there is substantial evidence, regardless of the patient's consent. He chastises psychiatry for its failure "to provide evidence for the efficacy of psychoanalysis and psychodynamic psychotherapies as treatments for psychiatric disorders." Although he acknowledges other kinds of evidence for efficacy, controlled clinical trials provide the key evidence. He writes, "Those treatments which make claims but have not generated evidence are in a weak position." Certainly, nothing in his paper indicates that he thinks there is substantial evidence for treatments in this weak position.

It is by no means certain that a psychiatric patient's informed consent would in fact insulate a psychiatrist. Malpractice is always a retrospective determination after an adverse outcome. Therefore, I believe the import of Klerman's recommendations can be understood by a reasonable lawyer as stating that, in the absence of new efficacy studies, exclusive use of psychoanalysis, psychodynamic psychotherapy, or, perhaps, other humanistic psychotherapies that are not scientifically substantiated is improper, in a weak position, and subject to serious, if not dispositive, challenge in any malpractice litigation. Those are the legal inferences I have drawn from Klerman's presentation. What follows, therefore, is based on that interpretation and will fur-

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ther demonstrate the basis for it. Hereafter, I will refer to psychoanalysis and psychoanalytic therapy as traditional psychiatry, recognizing, as does Klerman, that the psychoanalytic approach has been a dominant force in psychiatry in the United States since World War II.

## THE LAW

Klerman's title, "The Psychiatric Patient's Right to Effective Treatment," will suggest to most psychiatrists that the law has announced some new Constitutional right and that it has something to do with *Osheroff v. Chestnut Lodge*. However, as Klerman recognizes, this litigation was settled out of court. No Constitutional claim was made, and no judge formulated any legal theory about the so-called right to effective treatment. There is no clear legal precedent for anything Klerman states in his paper.

I have therefore carefully eschewed the phrase the "Osheroff case" to emphasize that there is no decided case establishing any relevant legal precedent about rights or about negligence in the law of Maryland or any other jurisdiction. (There was an arbitration report and a published decision on a narrow procedural question.) Furthermore, when Dr. Osheroff agreed to settle his legal claims, he undoubtedly signed documents indicating that Chestnut Lodge was not to be deemed negligent on any ground. Therefore, the legal precedent of the *Osheroff* litigation is unknown and unknowable. It does not exist.

Klerman also asserts that "the case has been widely discussed in legal journals." He then cites an article that began as required written work by Malcolm as a Harvard law student (2). This work has since been expanded into a book (3). Malcolm's article and an unpublished paper by Livingston are the only citations Klerman relies on for the legal implications he draws from *Osheroff*. It is totally without legal precedent and without any other legal authority or evidence that Klerman writes, "In my opinion, this case goes a long way toward establishing the patient's right to effective treatment." Particularly troubling is Klerman's use of the phrase "the right to effective treatment." Patients' rights usually refer to Constitutional or statutory rights. For instance, the familiar right to treatment is based on the Bill of Rights or on legislation. Klerman describes no such basis for this new right. Furthermore, Dr. Osheroff's litigation involved allegations of malpractice. With the exception of the so-called right to informed consent (4), malpractice law is not ordinarily conceptualized in terms of a patient's rights but about a physician's negligence (5). Legal scholars would certainly argue that even in negligence law and malpractice one can speak of every duty in terms of a countervailing right. Klerman, however, provides no legal basis for either a duty or a right. Klerman's concluding recommendations suggest that the right to effective treatment is somehow derived from the right to informed consent. That would be a radical legal

departure from existing law. Although the courts have broadened the legal requirements of disclosure in informed consent, their goal has always been to increase the patient's autonomy and not to regulate or restrict methods of treatment. Furthermore, empirical research suggests that the law of informed consent is already out of touch with clinical reality (6). Nonetheless, Klerman's recommendations would further expand and rigidly specify this legal obligation. In any event, the right to effective treatment is never clarified; its legal basis is never documented; its use is confused and confusing; and Klerman acknowledges that he has not confronted the legal complexities or consequences involved in informed consent, which vary from state to state according to statutes and case law (7).

Malpractice law quintessentially concerns duties translated into standards of care. The standard of care depends on the facts of the situation. Familiarity with a malpractice treatise would make it clear that it is difficult, if not impossible, to generalize about the standard of care in all of psychiatric practice based on one actual situation (5). Yet that is exactly what Klerman seems to be doing in making conclusions about the legal implications of *Osheroff*.

Once it becomes clear that there is neither legal precedent nor established legal authority for what Klerman writes here, it becomes possible to discern more clearly the nature of his paper. It is not about law; rather, it is an attempt to promulgate more uniform scientific standards of treatment in psychiatry, based on his own opinions about science and clinical practice. Klerman notes the large number of expert witnesses for Dr. Osheroff, including Drs. Donald Klein, Bernard Carroll, Frank Ayd, and himself. Their number is less impressive than their professional qualifications and their shared "scientific" perspective. This panel of experts certainly rivals in eminence any group that was ever assembled to testify on the patient's side of a malpractice case in psychiatry. None of them, however, is by reputation an authority on informed consent. They were all willing to testify on other grounds that Chestnut Lodge was negligent in its diagnosis and/or treatment. I take it that Klerman defends that testimony in his paper and suggests that his basic rationale should be accepted by like-minded colleagues who might testify in future malpractice litigation. Klerman's recommendations may have considerable legal consequences, even if his ideas have no basis in law and are intended only as clinical recommendations. The basic practical consideration for a contingency-fee lawyer in malpractice litigation is whether one or more expert witnesses can be found with sufficient professional authority who are willing to testify convincingly that their colleagues are guilty of negligence (5). Whatever claim a lawyer makes against a traditional psychiatrist can only be helped by any expert witness who accepts Klerman's opinions. For example, any traditional psychiatrist whose patient commits suicide might face expert testimony stating that the treatment provided was not proper and lacked substantial evidence of efficacy,

which could lead to liability. Thus, Klerman's paper has potentially serious legal consequences for all practitioners of traditional psychiatry.

#### THE STANDARD OF CARE IN OSHEROFF

Klerman clearly recognizes, and it must be emphasized, that the alleged malpractice in *Osheroff* took place in 1979. Therefore, the legal standard of care to be applied is the accepted practice of the psychiatric profession more than a decade ago. Much has happened in psychiatry in the past decade, both in our diagnostic approaches and in our treatment armamentaria. Those developments cannot be the basis for an expert witness's opinion about the standard of care in 1979. In his chapter on affective disorders in *The Harvard Guide to Modern Psychiatry*, published in 1978 (8), Klerman suggested the accepted practices of the time. Two things should be noted about this chapter. First, he recognized that many respectable clinicians held to a unitary (psychoanalytic) theory of mental illness in general and of depression in particular but that he had himself accepted the concept of "multiple symptom complexes" as the more enlightened approach to nosology. Second, although he clearly favored combined chemotherapy and psychotherapy and a pluralistic approach to etiology and treatment, Klerman wrote, "Individual psychotherapy based on psychodynamic principles remains the most widely used form of psychotherapy. Although systematic, controlled clinical studies do not exist, clinical observations strongly support the value of this form of psychotherapy during both acute and long-term treatments." He even suggested that traditional psychoanalysis might be "indicated for neurotic depressions in individuals with longstanding personality disorders." Thus, Klerman's own 1978 publication summarizing what was known then about affective disorders would by itself go a long way as a legal defense of Chestnut Lodge. Ironically, except for the word "strongly," his revised chapter in the 1988 *New Harvard Guide to Psychiatry* (9), quoted at the end of this paper, contains almost identical language.

It is essential that the reader distinguish between the narrow legal question of what was negligent in 1979 and the much broader arguments about scientific evidence and policy advanced by Klerman. He attempts to link together the *Osheroff* litigation, the legal standard of care in malpractice, efficacy research, and public policy based on efficacy research. It is possible to argue that he presents each of these issues and their supposed connections in a one-sided and partisan fashion. Therefore, I shall here present the other side. First, if there was malpractice in *Osheroff*, the strongest argument is that under the facts of that case, as described by Klerman, negligence arose from the persistence in a course of exclusive psychodynamic treatment despite obvious psychotic deterioration. This argument does not depend on the latest scientific research on efficacy or the scientific status of psychoanalysis or psychody-

namic psychotherapy. Second, the legal standard of care in malpractice is not and should not be a universal rule set by one school of psychiatry for the others, even if it wraps itself in the mantle of modern science. Rather, the legal standard of care should reflect the "collective sense of the profession" (10), not the partisan opinions of one particular group and certainly not the latest unreplicated and evolving scientific evidence (5). Third, efficacy research, including controlled clinical trials, is of varying quality. Much of it is far from being based on solid methodological grounds (11), and the leap from controlled trials to clinical practice often produces unexpected results. Public policy based on such a limited scientific foundation and enforced by malpractice litigation is unlikely to benefit our patients or our profession. If the kind of efficacy research now available to psychiatry led to decisively beneficial treatment for most patients with minimal side effects and long-term improvement, there would be no professional debate. However, it should be obvious that all of Klerman's arguments about law, science, efficacy, and policy stand or fall without regard to the *Osheroff* litigation.

#### A RESTATEMENT OF THE CASE HISTORY

Klerman's brief description of Dr. Osheroff's history makes the diagnosis of narcissistic personality disorder seem ridiculous. The details of Dr. Osheroff's case history, including excerpts from his own autobiographical account, have been published by Malcolm (3) and are the basis for what follows here. I have no professional relationship with Dr. Osheroff or the litigation. Furthermore, I would emphasize that everything reported here is available to the general public in Malcolm's book. There are still reasons to have qualms about republishing the personal details of an identified patient's case history. On the other hand, Klerman has made this case the centerpiece of his paper and Dr. Osheroff himself participated in a session at the 1989 APA annual meeting.

Malcolm's book reports that Dr. Osheroff was married three times before his hospitalization. His first marital relationship began while he was in college and ended in divorce after 21 months because his wife had allegedly been unfaithful. He thought of leaving medical school but saw a psychiatrist who convinced him to return. During his internship he met and married a nurse. That second marriage lasted much longer but deteriorated after the birth of two children. Dr. Osheroff saw a psychiatrist again during these years while he was establishing his practice. According to Malcolm (3), he wrote about this period of time in his autobiography, which he entitled *A Symbolic Death*:

All during the early years of my [second] marriage, I had been rather immature and insensitive and my energies seemed to be so devoted to and focused on my career, that I perhaps was not listening and if I was listening, perhaps



I wasn't hearing. I was seemingly oblivious to the stresses that were developing in my marriage at the time.

Psychotherapy for Dr. Osheroff and marital therapy for the couple did not save the marriage. His second wife eventually left the children with him and went off with another man. Dr. Osheroff lost 40 pounds during this time, living "a life that was almost devoid of the usual types of satisfaction." His nephrology practice, nonetheless, grew and prospered as he opened his own dialysis center. He then met his third wife, a medical student on her clinical clerkship, and married her after a "whirlwind romance." This was at first a happy and successful marriage, and symptoms of depression apparently disappeared. He and his wife were, in his words, "one of the most celebrated and sought after medical couples in the . . . area."

There were continuing conflicts, however, with his second wife, who now wanted custody of their two children. Conflicts also began with his third wife. They were precipitated, according to her, by his seemingly inconsiderate behavior during the birth of their first child (his third) and his lack of attention to the baby and her.

Dr. Osheroff also began to have serious disagreements with his professional associates in practice. With these conflicts and the deterioration of his third marriage, he saw at least three different psychiatrists, two of whom prescribed antidepressive medication, which was not successful—perhaps because of lack of compliance. It is well recognized that "drug manipulation and drug compliance are anticipated problems" in patients whose affective symptoms are complicated by personality disorders (12). No doubt, such problems can be even greater when the patient is himself a physician and may have his own opinions about treatment.

I do not mean to suggest that Klerman intentionally selected from the history only those features which support his diagnosis and the basic thesis of his paper. Perhaps the kinds of subjective experiences revealed in Dr. Osheroff's autobiographical account and the interpersonal difficulties he experienced with the important people in his life, which suggest problems in the sphere of object relations and character, have become less relevant to psychiatrists who tend to overemphasize *DSM-III*'s axis I in comparison with axis II. Perhaps these two quite different histories indicate that there is an incorrigible diagnostic and conceptual difference between Klerman's school and traditional psychiatrists. The "scientific" psychiatrist now looks for the symptoms. The traditional psychiatrist still looks for the person. Each school can criticize the blindness of the other on the basis of its own criteria.

In any event, when Dr. Osheroff entered Chestnut Lodge he was not a neophyte as to psychiatry or its various therapeutic approaches, nor was he professionally or personally ignorant about depression. He was a physician who, I have no doubt, had already several times in his life been diagnosed, fully informed about his diagnosis, and treated exactly in the manner recommended by Klerman in his paper. Those treatment methods had

failed. All of this seems relevant to any judgment about Chestnut Lodge's alleged negligence and the lessons Klerman claims are to be learned from this litigation.

## THE DIAGNOSIS

Klerman relies on a strict construction of *DSM-II*, *DSM-III*, and *DSM-III-R* in his discussion of the standard of care for diagnosis. He points out that there was no narcissistic personality disorder in *DSM-II*. Therefore, Chestnut Lodge used a diagnosis not listed in psychiatry's official nomenclature.

*DSM-II*, however, was certainly not regarded with the same authority the profession has given its successors. Psychodynamic etiological diagnoses were commonly used whether or not they were in *DSM-II*, and narcissistic personality was perhaps the most frequently used. Indeed, it became the diagnosis of an entire culture (13). Given my restatement of the case history, I believe that the vast majority of psychiatrists would agree that a diagnosis of narcissistic or some other personality disorder at the time of admission was not evidence of negligence, particularly since a diagnosis of affective disorder was also made. Most psychiatrists in 1979 would not have considered it a breach of professional standards merely to depart from official nomenclature in this way.

Dr. Osheroff's own autobiographical account of his illness would substantiate many, if not all, of the typical features of narcissistic personality disorder described by Kernberg (14). Certainly, the restated case history presents relevant evidence omitted by Klerman.

## THE TREATMENT

The breakdown of Dr. Osheroff's third marriage and his professional conflicts, which precipitated his hospitalization, could reasonably have been understood at the time as classic examples of the kind of psychosocial crises that destroy the precarious balance of the narcissistic personality. Even if Klerman believes that this kind of psychodynamic formulation and approach to treatment is no longer "scientifically" acceptable, there can be little doubt that it was well within the collective sense of the profession in 1979. Thus, I suggest that the initial treatment program for Dr. Osheroff was acceptable, particularly in the light of a history of previous unsuccessful drug treatment provided by a leading psychopharmacologist and implemented by his traditional psychotherapist.

With only this psychodynamically oriented psychotherapy, however, the patient's condition obviously deteriorated. Whatever the original diagnosis and treatment plan were, reevaluation and consultation are required at some point when a treatment regimen has such obviously negative consequences. I have no doubt that during the 1950s, 1960s, and 1970s at Chestnut Lodge and other similarly oriented hospitals, tradi-

tional therapists did persist in exclusive psychoanalytic psychotherapy, despite similar situations of obvious symptomatic deterioration. My own clinical experience at McLean Hospital during these years certainly confirms this impression.

If Klerman had stayed with this narrow fact of the situation and stated that exclusively psychoanalytic treatment of a hospitalized patient in the face of obvious psychotic deterioration is no longer clinically acceptable, I believe he could have claimed to speak for the collective sense of the profession, including the vast majority of traditional psychiatrists.

It is important to recognize that this marks an important historical moment of transition in modern psychiatry. Many new considerations as well as efficacy studies have led to this change. The biological dimensions of serious mental disorders and their treatment have been better understood, and this understanding has been more widely accepted. The consequences of long periods of psychotic decompensation have been more fully recognized. The distinction between social recovery with improvement of symptoms and the cure of serious mental illnesses has been better appreciated, and psychiatric hospitalization has increasingly focused on the former. The negative implications of long-term hospitalization of patients with psychotic disorders have been well documented. Psychiatrists have recognized the importance of improvement in symptoms for the therapeutic alliance and, therefore, as a necessary part of treatment with seriously disturbed patients. The limitations of traditional therapy with psychotic patients are widely accepted, and successful treatment is more often attributed to the unique qualities of the therapist or the relationship rather than to the method of the psychotherapy. All of these factors and not just the available efficacy studies have led to the changes in the collective sense of the profession.

At Chestnut Lodge, Dr. Osheroff apparently developed a negative therapeutic reaction and a negative transference to both the therapist and the hospital. The person suffering from these serious symptoms of depression was in revolt against his treatment. The recommendation to change hospitals seems to me eminently sound on psychodynamic grounds. Klerman suggests that Dr. Osheroff's remarkable cure at the Silver Hill Foundation was a function of his finally being provided the efficacious combination of tricyclics and phenothiazines. If all patients like Dr. Osheroff had such remarkable cures with these drugs, psychiatry would be a different profession. But Dr. Osheroff's psychological response to Silver Hill Foundation, as described in his autobiography, suggests that other, equally important, psychodynamic factors were involved. He had escaped, if not narcissistically triumphed over, Chestnut Lodge and his therapist. His negative transference had been vindicated. Such psychodynamic conceptions still seem as relevant to our clinical understanding of such remarkable cures as does psychopharmacology.

## BIOLOGICAL VERSUS PSYCHODYNAMIC PSYCHIATRY

Klerman and Klein have both objected to my characterization of the *Osheroff* dispute as one between biological and psychodynamic psychiatry (15). Klerman here states that it is, rather, a matter of opinion versus evidence. Klein (16) has made the same point in stronger and more colorful language. Both of them contend that they are speaking as scientists and that the issue is one of scientific evidence versus dogmatic opinion. Klerman makes this a thesis of his current paper, applying it as a standard to all psychiatric treatments. I believe that both men ignore the very real problem of differing opinions about scientific evidence and the canons of science within the psychiatric profession. Klerman and Klein surely recognize that the quality of the evidence, even in their own impressive research, leaves room for other scientists to make interpretations and raise questions. The basic assumptions on which clinical research on depression and manic states proceeds are subject to fundamental questions by serious scientists (17). Klerman is no doubt correct that at a meeting of scientists, the person with evidence should take precedence over the person without evidence. Even a small amount of evidence is better than opinion when the question is what can science say about a subject. But that does not mean the science is good enough to create a uniform policy or to dictate to clinicians the clinical standards of care.

Klerman also objects to the "biological" designation because of his longstanding pluralistic approach to etiology and treatment. My intention, however, was not to suggest that he was a biological psychiatrist but that he brought a biological perspective, as opposed to the psychodynamic perspective of Chestnut Lodge, to the *Osheroff* dispute. My objective was to explain what I understood to be the basis of the dispute. Certainly, if I had been responsible for Dr. Osheroff's care I would have insisted on "biological treatment" in the face of obvious psychotic deterioration. It has been my longstanding contention that in similar actual situations, judges upholding the right to refuse treatment were forcing psychiatrists to commit malpractice (18). Unfortunately, Klerman's paper goes well beyond the facts of *Osheroff*. His standards are meant to apply to the treatment of any *DSM-III-R* disorder, and the onus he places on traditional psychiatry is unmistakable.

## EFFICACY RESEARCH AND PUBLIC POLICY CONCERNS

There is an apocryphal story told about male lawyers. One asks the other, "How is your spouse?" The other replies, "Compared to what?" "Compared to what" is the appropriate perspective to bring to Klerman's discussion of efficacy research and policy. He compares psychotherapy and drugs. In that comparison he criticizes the failure of various government agencies at the federal and state levels. He also criti-



cizes his colleagues in research and in professional associations. When compared to Food and Drug Administration safety and efficacy standards for drugs, the regulation of psychotherapy seems to stand out as a public policy disaster. But virtually everything Klerman says about psychotherapy applies with equal force to surgery and almost everything else that physicians do which does not come under the Food and Drug Administration's authority. Much of what all physicians do has no demonstrated effectiveness—even the prescription of supposedly efficacious medication. Thus, if psychotherapy is compared to surgery, for example, one might get a totally different impression about the nature and significance of the public policy problem posed by traditional psychotherapy. It turns out that the Food and Drug Administration is quite unique, holding the massive pharmaceutical industry hostage and able to require it to invest vast resources in research into efficacy and safety. Thus, Klerman's use of the Food and Drug Administration as a model is less relevant and less meaningful than it seems.

All health policy experts are concerned about efficacy. Indeed, efficacy research has become the central requirement of what Relman (19) called the third revolution in medical care, requiring increased attention to assessment and accountability. In order to meet the pressing objectives of quality and cost control, however, Relman wrote, "We will also need to know much more about the relative costs, safety, and effectiveness of all the things physicians do or employ in the diagnosis, treatment and prevention of disease" (19). Relman was commenting on an article by Roper et al. (20) of the Health Care Financing Administration, who described new "effectiveness initiatives." These will increasingly involve the federal government in the collection and distribution of efficacy and outcome data concerning many branches of medicine. Roper et al., along with Relman, stated that more comprehensive assessment of medical effectiveness will eventually improve the quality of care and eventually help curtail costs. Unlike Klerman, they suggested that the science of efficacy research currently available in the rest of medicine is inadequate to the task. The focus of the Health Care Financing Administration was on surgery. For example, they cited carotid endarterectomy and the implantation of cardiac pacemakers as examples of surgical practices often used inappropriately because of the lack of adequate efficacy studies. More money is certainly spent on these procedures than on all of the traditional psychotherapy provided in the United States—and the immediate risks of their use or misuse are much greater. Roper et al. (20) clearly recognized what Klerman has not: that the "science of health care evaluation, still in its formative stages, requires certain resources: money, data, and people trained in the evaluative sciences" and that "methods of gathering and synthesizing data on health outcomes and effectiveness are correspondingly underdeveloped."

Roper et al. made it clear that a whole new infrastructure for gathering data is necessary before sensible

public policy can be developed to control clinical practice. They did not blame the medical profession for this gap in our scientific knowledge. Klerman's paper, in contrast, seems to be a rush to judgment, with the first stop at the courthouse. Klerman does not even acknowledge that there is any legitimate opposition to his views. He is prepared to argue that "the absence of professional consensus statements in our field leaves it open for the courts to be used by individuals, such as Dr. Osheroff, who feel they have been poorly treated and who believe they are entitled to redress of their grievances." This is to suggest that the psychiatric profession is now being punished for its own sins of laxity, which opened the door to the courtroom. This is simply nonsense. Every legal scholar writing on the subject of psychiatric malpractice has pointed to the lack of professional consensus in psychiatry as a major cause for the remarkable dearth of such litigation compared to other specialties over the past century (5, 21). In fact, any experienced lawyer would say that Dr. Osheroff was able to litigate because he was able to obtain expert witnesses like Klerman and his distinguished colleagues, who were willing to testify that there is a consensus about efficacious treatment. Indeed, Klerman's paper is an attempt to assert and establish this thesis.

The use of the courtroom and malpractice litigation to enforce a consensus policy on efficacy would have serious consequences for biological psychiatry as well as for the field as a whole. The history of neuroleptic medication for schizophrenic disorders presents a striking example. Psychiatry's understanding of efficacious doses and deleterious side effects has changed dramatically over the past two decades. We have gone from smaller doses to megadoses back to smaller doses. We have gone from routine maintenance to selective maintenance. We went through a brief phase of rapid intramuscular "neurolepticization" for acute psychotic disorders and abandoned it (22). All of these changing standards of care were based on clinical experience, available scientific evidence, and a genuine concern for providing effective treatment. If, at any early point in this history, biological psychiatrists had gone to court or to any other official authority to impose efficacious dose standards on all their colleagues, it would have been a disaster for our patients and for biological psychiatry. If it is Klerman's idea that psychiatry should be ruled by the courts applying the prevailing scientific evidence of the day, he has a recipe for disaster.

#### KLERMAN'S SPECIFIC RECOMMENDATIONS

##### *Responsibility to Make a Diagnosis According to DSM-III-R*

*DSM-III* and *DSM-III-R* constitute officially recognized diagnostic nomenclature. Furthermore, the use of this nomenclature is now widely accepted in the profession. Thus, Klerman's first recommendation is

not obviously controversial. Looking back to the *Osheroff* litigation, Klerman strongly objected to the diagnosis of narcissistic personality disorder based on psychodynamic considerations. Presumably, this requirement is intended to prevent similar lapses. Traditional psychiatrists writing in modern psychiatric textbooks continue to emphasize psychodynamic formulations and criticize *DSM-III* and *DSM-III-R*. Nemiah (23), for example, wrote, "The new nomenclature and diagnostic grouping are a mixed blessing, particularly if one wishes to go beyond purely phenomenological description to a consideration of the psychodynamic mechanisms involved in the formation of symptoms—an activity that the framers of *DSM-III* would like to discourage." Klerman would not only discourage such activity but also delegitimize the psychodynamic diagnostic formulations of traditional psychiatry. The essence of the first responsibility is that it locks the traditional psychiatrist into the scientific paradigm urged by Klerman.

### *Responsibility to Inform the Patient*

Having made a diagnosis, the psychiatrist would be required to communicate it to the patient in a manner consistent with *DSM-III-R*. Ironically, Klerman cites me as supporting this requirement. I value *DSM-III-R* as a basis for more reliable communication within the psychiatric profession. I do not believe that all of its diagnostic categories have scientific validity or that they all have value in helping patients to understand their human problems or their mental disorders. Some *DSM-III-R* diagnoses seem quite helpful in this respect, and others do not. For some patients a psychodynamic diagnostic formation may be more helpful. Even when the diagnosis is helpful to the patient, there is the matter of timing, which Klerman fails to emphasize.

It is certainly my belief that psychiatrists should view helping patients understand their problems as one of their professional responsibilities. In that sense, informed consent is an essential goal and principle of psychiatry and of all psychiatric treatments. It is a predicate for a therapeutic alliance. But informed consent is a process, not an immediate one-time recitation of a formula regardless of the actual situation. *DSM-III-R* may or may not be helpful in that enterprise and therefore ought not to be forced on all patients by a blanket rule that places the clinician in a pseudoscientific ideological straightjacket. We should not confuse the valuable function *DSM-III-R* serves in clarifying communication among psychiatrists with its value in communication with our patients. Whatever the law of informed consent may be, it does not require uniform behavior in every actual situation. The law requires a reasonably prudent physician (5), not a scientific automaton. Klerman's criteria suggest an emphasis on controlling his colleagues rather than on promoting a therapeutic relationship.

### *Responsibility to Describe Alternative Treatments*

The psychiatrist, having made a *DSM-III-R* diagnosis and revealed it to the patient, is next required by Klerman to discuss with the patient the efficacious treatment alternatives. The burden here is heaviest on traditional psychiatrists, whom Klerman now relegates to a respectable minority. ("This is a special requirement on the respectable minority of physicians, since they should inform the patient that their treatment is not the one most widely held within the profession.") Klerman is prepared to abolish the legal concept of the respectable minority on scientific grounds. He seems not to recognize that this legal concept is intended, among other things, to protect scientific innovation against rigid orthodoxy in standards of care. Thus, the concept has no specific numerical definition (5). Relying on Livingston's unpublished student paper, Klerman selects 10% as a numerical definition of the legal concept. He suggests that traditional psychiatrists comprising such a respectable minority (although he provides no empirical evidence about their actual numbers) have a special burden. The burden seems to be to familiarize themselves with the claims of scientific efficacy put forward by all other therapies, present them to the patient, and inform the patient that their own traditional psychotherapy has no demonstrated efficacy.

I first injected the idea of the respectable minority into the *Osheroff* controversy from quite a different perspective (15). The question I had addressed was whether a hospital could hold itself out as providing exclusively psychoanalytic and psychosocial treatments for patients who had serious mental disorders under the respectable minority rule. The rule, despite its legal ambiguity, seemed to recognize that the practice of medicine was characterized by different schools of thought, not by uniform orthodox criteria (5). I assumed that such a hospital would accept only patients who chose not to have drug treatment or ECT. Klerman's deposition in the *Osheroff* litigation (3) seemed to indicate that in his expert opinion such a hospital would be negligent per se. This is by no means an entirely obsolete question, since advertisements apparently describing such a hospital have regularly appeared in the *American Journal of Psychiatry* (for instance, in the January 1989 issue, page A14).

If the respectable minority rule in law and other legal doctrine relevant to the necessary qualifications of experts have any role at all, it is to protect the diversity of reasonably prudent professional opinion and different approaches to the practice of the healing arts (5) against the rigid orthodoxy proposed by Klerman. Similarly, organized psychiatry, when it accepted *DSM-III*, specifically indicated that this was not intended as an endorsement of any etiological theory or therapy of mental disorder. Rather, it was agnostic, recognizing the diversity of professional views and opinions. Klerman's criteria for professional responsibility would repudiate the traditional commitment of both the law and psychiatry to diversity. It would fur-



ther narrow the practice of psychiatry and the choices available to patients. In his quest for efficacious standards, Klerman endorses an authoritarian control of psychiatric practice. The lessons of the history of science suggest that this would be detrimental, even to the aspirations of "scientific psychiatry."

### *Responsibility to Provide Proper Treatment*

Klerman's definition of a responsibility to provide effective treatment drives home the nails on the coffin he has devised for traditional psychiatry. He says, "The patient has the right to the proper treatment. Proper treatment involves those treatments for which there is substantial evidence." His paper makes clear that he believes there is no such substantial evidence for traditional psychotherapy in the treatment of any *DSM-III-R* disorder. Thus, psychiatrists who apply traditional psychotherapy cannot claim to provide effective treatment or to fulfill the patient's "right" to proper treatment. This criterion alone, given his arguments, might well raise the specter of malpractice, not for a respectable minority but for the majority of psychiatrists in the United States who at least in some of their practice provide such treatments to patients with *DSM-III-R* diagnoses. I again emphasize the point that if anything should go wrong during such treatment the claim could be made under Klerman's criteria that the therapist had failed to provide proper treatment.

The special burden placed on traditional psychiatrists by Klerman cannot be fully appreciated if one does not consider the quite different impact of these criteria on psychiatrists specializing in psychopharmacology. They can take Klerman's paper as authority for the proposition that they need never discuss or refer a patient for traditional therapy, since such treatments have no demonstrated efficacy compared to their own. Thus, they need to do nothing further to familiarize themselves with these unscientific theories and therapies. Furthermore, they need have no concern about their own responsibility to provide proper therapy. Klerman seems to accept Food and Drug Administration approval of efficacy as a sufficient minimum guarantee of proper treatment to appropriate patients. Thus, all standard psychopharmacology is by definition proper. Ironically, it is not at all uncommon in the treatment of panic disorder, the example given by Klerman, for different psychopharmacologists to reach contradictory conclusions about the relevant scientific literature on the basis of their judgment and professional opinion. Klerman has no intention of preventing these colleagues from telling patients that despite demonstrated efficacy, Food and Drug Administration approval, and widespread use a particular drug is worthless and even dangerous in their opinion. It is only traditional psychiatrists who are not permitted to have such professional opinions about scientific evidence.

### *Responsibility to Consult and Refer*

There is a great deal of law as well as ethical principles in psychiatry that establish a responsibility to seek expert consultation when a patient's condition obviously deteriorates on a given regimen of treatment (5, 24). Psychiatrists have not always respected this legal and ethical requirement, perhaps because, as Klerman suggests, they have failed to recognize the safety and efficacy of alternative treatments. If Klerman had made this the central feature of his discussion of the facts of the *Osheroff* litigation and its implications for psychiatry and for legal policy, there would have been no need for a response.

### CONCLUSIONS

If it is correct that Klerman's arguments and recommendations are not required by law or by any legal precedent of *Osheroff*, then it would appear that Klerman is invoking the threat of malpractice liability to further his own "scientific" approach and his own vision of what clinical psychiatry is and should be. This strategy of seeking legal empowerment is an unfortunate and increasing tendency in the psychiatric profession. Advocates of various partisan positions in psychiatry have gone to the courtroom and to the law to advance their own schools and ideologies. It is striking to me how often legal decisions that offend the psychiatric profession as a whole are based on the expert opinions of psychiatrists advocating their own partisan positions. The psychiatric profession has often complained about the constraints the law was placing on us and our patients (25). What we have failed to recognize is how often what the law did was based on the partisan and adversarial testimony of our colleagues. We have less reason to fear our litigious patients and their lawyers than our partisan colleagues in this new era of psychiatric malpractice. Unfortunately, Klerman has chosen to attack traditional psychiatry in the context of a legal dispute and in a manner that may have consequences he did not intend. Law is a blunt instrument; it can be used to beat down the opposition, but no one should think that the law can chart the path of scientific progress in clinical psychiatry.

Klerman has often been able to speak for the collective wisdom of the psychiatric profession. His own words, in *The New Harvard Guide to Psychiatry* (9), are the best answer in the courtroom to the partisan position he has asserted here: "Individual psychotherapy based on psychodynamic principles remains the most widely used form of psychotherapy. Although systematic, controlled clinical studies do not exist, clinical experience supports the value of this form of treatment."

## REFERENCES

1. Klerman GL, Weissman MM, Rounsaville BJ, et al: Interpersonal Psychotherapy of Depression. New York, Basic Books, 1984
2. Malcolm JG: Treatment choices and informed consent in psychiatry: implications of the Osheroff case for the profession. *J Psychiatry Law* 1986; 14:9-107
3. Malcolm JG: Treatment Choices and Informed Consent: Current Controversies in Psychiatric Malpractice Litigation. Springfield, Ill, Charles C Thomas, 1988, pp 22-37
4. *Canterbury v Spence*, 464 F 2d 772 (DC Cir 1972)
5. Louisell DW, Williams H: *Medical Malpractice*, rev ed. New York, Matthew Bender, 1983
6. President's Commission for the Study of Ethical Problems in Medicine and Biomedical Research: Making Health Care Decisions, vol 2: Appendices. Washington, DC, US Government Printing Office, Oct 1982
7. President's Commission for the Study of Ethical Problems in Medicine and Biomedical Research: Making Health Care Decisions, vol 3: Report. Washington, DC, US Government Printing Office, Oct 1982
8. Klerman GL: Affective disorders, in *The Harvard Guide to Modern Psychiatry*. Edited by Nicholi AM Jr. Cambridge, Mass, Belknap Press (Harvard University Press), 1978
9. Klerman GL: Depression and related disorders of mood (affective disorders), in *The New Harvard Guide to Psychiatry*. Edited by Nicholi AM Jr. Cambridge, Mass, Belknap Press (Harvard University Press), 1988
10. King JH: *The Law of Medical Malpractice*. St Paul, West, 1986, p 51
11. Elkin I, Pilkonis PA, Docherty JP, et al: Conceptual and methodological issues in comparative studies of psychotherapy and pharmacotherapy, II: nature and timing of treatment effects. *Am J Psychiatry* 1988; 145:1070-1076
12. Cole JO, Sunderland PS III: The drug treatment of borderline patients, in *Psychiatry 1982: The American Psychiatric Association Annual Review*. Edited by Grinspoon L. Washington, DC, American Psychiatric Press, 1982
13. Lasch C: *The Culture of Narcissism: American Life in an Age of Diminishing Expectations*. New York, Warner Books, 1979
14. Kernberg OF: An ego psychology and object relations approach to the narcissistic personality, in *Psychiatry 1982: The American Psychiatric Association Annual Review*. Edited by Grinspoon L. Washington, DC, American Psychiatric Press, 1982
15. Stone AA: The new paradox of psychiatric malpractice. *N Engl J Med* 1984; 311:1384-1387
16. Klein DF: The *Osheroff* case: a rebuttal. *Psychiatr News*, April 7, 1989, p 26
17. Baldessarini RJ: Update on recent advances in antidepressant pharmacology and pharmacotherapy, in *Psychobiology and Psychopharmacology*. Edited by Flach F. New York, WW Norton, 1988
18. Stone AA: *Law, Psychiatry, and Morality: Essays and Analysis*. Washington, DC, American Psychiatric Press, 1984
19. Relman AS: Assessment and accountability: the third revolution in medical care (editorial). *N Engl J Med* 1988; 319:1220-1222
20. Roper WL, Winkenwerder W, Hackbarth GM, et al: Effectiveness in health care: an initiative to evaluate and improve medical practice. *N Engl J Med* 1988; 319:1197-1202
21. Furrow BR: *Malpractice in Psychotherapy*. Lexington, Mass, Lexington Books, 1980
22. Kane JM: Somatic therapy, in *Psychiatry Update: American Psychiatric Association Annual Review*, vol 5. Edited by Frances AJ, Hales RE. Washington, DC, American Psychiatric Press, 1986
23. Nemiah JC: Psychoneurotic disorders, in *The New Harvard Guide to Psychiatry*. Edited by Nicholi AM Jr. Cambridge, Mass, Belknap Press (Harvard University Press), 1988
24. American Psychiatric Association: *The Principles of Medical Ethics With Annotations Especially Applicable to Psychiatry*, rev ed. Washington, DC, APA, 1981
25. Stone AA: The myth of advocacy. *Hosp Community Psychiatry* 1979; 30:319-322



## Whatever Happened to Intensive Psychotherapy?

Kenneth Z. Altshuler, M.D.

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*Of 163 residency programs responding to a survey about training requirements in long-term psychotherapy, more than 100 did not require that any patients be seen more than once a week. Among 41 psychotherapy protocols representing outcome-related research that were reported at an annual meeting of the Society for Psychotherapy Research, the studies employing more than once-a-week treatment for 6 or more months were rare. Intensive psychotherapy is clearly on the wane in training programs and in psychotherapy research paradigms.*

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From the mid-1940s through the late 1960s, before the biological revolution took hold, intensive psychotherapy was a major tool in psychiatry's armamentarium (1). Psychiatric residents in the course of their training saw several patients two, or even three, times a week in psychotherapies that often endured for years. Progress in biological psychiatry and the failure of psychoanalysis to demonstrate its efficacy have moved intensive psychotherapy from its place center stage. This paper reports a small effort to see where it stands now.

### METHOD

The essentials of psychiatry residency training mandate an experience in individual, long-term psychotherapy (2). A total of 212 psychiatry residency programs

were surveyed to determine how this requirement is met. Programs were selected from the *Directory of Psychiatry Residency Training Programs* (3) and from the 1988-1989 directory of training directors of the American Association of Directors of Psychiatric Residency Training so as to sample each training program (e.g., university program) once rather than inquire of each of several hospitals within a given program. The survey asked how many patient hours a week of psychotherapy were required in the third and fourth years and what number of outpatients had to be seen in once-a-week, twice-a-week, or more than twice-a-week therapy.

The object was to determine the range and maximum number of patient hours required for psychotherapy in any year of a program, whether an experience in intensive psychotherapy was included, and what it was. Responders almost uniformly required a psychotherapy experience in both the third and fourth postgraduate years, and for the most part the requirements were similar. In the tabulations which follow, only one number is reported—that for both years if the 2 years were identical and that for the year with the greater requirement if the 2 years of a program were different. An occasional program reported that the psychotherapy experience began in postgraduate year 1; no particular note is made of these instances. Similarly, since the search was for what was required, the lower number was tabulated when responses noted that "one or two" or "two or three" patients had to be seen in a specified frequency of treatment.

A second survey was sent to the 45 individuals presenting papers at the 1988 annual meeting of the Society for Psychotherapy Research whose abstracts indicated an attempt to measure process or outcome of therapy (4). Questions focused on the type of therapy (e.g., brief dynamic, cognitive, interpersonal, psychoanalytic), its frequency and form (e.g., individual or group), and the number of sessions and weeks or months that it lasted. If the response included a comparison therapy, similar questions were asked about it,

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Received May 23, 1989; revision received Sept. 6, 1989; accepted Oct. 6, 1989. From the Department of Psychiatry, University of Texas Southwestern Medical Center at Dallas. Address reprint requests to Dr. Altshuler, Department of Psychiatry, University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Blvd., Dallas, TX 75235-9070.

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**TABLE 1. Requirements of 163 Psychiatry Residency Programs Concerning Frequency and Amount of Psychotherapy**

Required Hours of Psychotherapy per Week	N	Required Frequency			
		None or Once a Week or Less (N=101)		More Than Once a Week (N=62) <sup>a</sup>	
		N	%	N	%
Less than 4	45	38	37.6	7	11.3
4-6	31	19	18.8	12	19.4
7-9	24	15	14.9	9	14.5
10 or more	63	29	28.7	34	54.8

<sup>a</sup>These programs tended to require more psychotherapy experience generally than programs that required psychotherapy once a week or less ( $p < 0.0001$ , Wilcoxon rank-sum test).

and the treatment was counted as another therapy study.

## RESULTS

Of the 212 questionnaires mailed to psychiatry residency programs, 163 were returned with enough information to be counted. Among nonresponders, no bias was apparent in such factors as regional distribution, urban versus rural location, or public versus private support. All but nine of the responding programs required a psychotherapy experience in the third and fourth years; eight required it in the third year only and one in only the fourth year. In terms of patient hours required, the range was from 2 to over 20 per week. Table 1 presents data on the number of programs requiring less than 4, 4-6, 7-9, and 10 or more patient contact hours per week in psychotherapy.

Of greater interest, perhaps, is a look at the data from the standpoint of what intensity was required in the psychotherapy training experience. Of the 163 respondents, over 60% indicated that only once-a-week psychotherapy was required or that there were no requirements at all with regard to the frequency with which patients were seen. Less than 40% required an experience in psychotherapy twice a week or more; of these, 21 programs required one twice-a-week experience, 28 required two twice-a-week treatments, seven required that three patients be seen twice a week, one required that four patients be seen twice a week as necessary, and two required that five patients be seen at the latter frequency. One program required that three patients be seen three times a week, and two required that four patients be seen four times a week, during at least one of the residency training years. As table 1 reveals, programs requiring that patients be seen more often than once a week also tended to require more psychotherapy experience generally than those with less intensive requirements.

Society for Psychotherapy Research respondents reported 34 studies of individual psychotherapy. Twen-

ty-eight were studies of once-a-week therapy. Of these, 25 studied treatments lasting 6 months or less (in addition to one open-ended study, one in which treatment endured for a year, and one in which treatment lasted for 8 months). Only six studies consistently used more than once-a-week treatment in their protocols. One was for 10 weeks and two were for 12 weeks; one was a psychoanalytic study of one patient; one was open-ended, treated patients either once or twice a week, and aimed at relating such qualities as the therapeutic bond and self-relatedness to outcome; in the last study patients were seen once, twice, or three times a week from 16 weeks to 8 years, and patients' and therapists' views of outcome were studied in relation to techniques and style of therapeutic relationship. Seven additional studies reported outcome variables in group therapy. All involved treatments of once a week or less; one lasted for 6 months and six for less.

## DISCUSSION

A few observations must be brought to bear on the interpretation of these data. Psychoanalytic or intensive, psychoanalytically oriented studies of change, when they were done, rarely focused on symptoms. Instead, interest was on conflict resolution and rearrangement of defensive structure, both of which defied objective measurement. The major symptom-related study indicating a failure of this kind of treatment was one aimed at measuring the success of psychoanalysis with schizophrenia (5). In contrast to the abundance of scientific studies of cognitive therapy and interpersonal therapy, or even of brief dynamic therapy of various sorts (6-8), a search of the literature of the last 15 years yielded no studies of psychoanalysis or extended, psychoanalytically oriented treatment aimed at symptoms of depression, for example, or in which results were measured by changes on such instruments as the Beck or Hamilton depression scales or the Global Adjustment Scale.

Statements that intensive psychotherapy has not proved effective are easy to find (9-11). Such assertions, while true, are misleading. The meta-analysis of psychotherapy's effectiveness by Smith et al. (12) surveyed as its base 475 studies that met at least minimal scientific standards. Not one was a study of psychoanalysis or of intensive (e.g., two times weekly or more), long-term (e.g., a year or more) psychotherapy. Similarly, the Garfield and Bergin review of studies relating frequency of visits to outcome (13) listed no studies of adults seen twice a week or more, enduring more than 6 months, and using modern measures. Thus, it would appear that the question of effectiveness outside of schizophrenia has never been tested (14), and the long history of intensive psychotherapy's failure to demonstrate its effects has been mistaken—as even Eysenck (15) noted—to mean proven ineffectiveness.

It is clear that not only psychoanalysis but extended,



intensive psychotherapy has lost ground and favor in psychiatry residency training programs and research. The Tasman and Kay survey of resident training in 1986 (16) noted this situation, although it did not report requirements of frequency or duration in the psychotherapy training experience. The task force formed by the Association for Academic Psychiatry and the American Association of Directors of Psychiatric Residency Training recognized the changing state of affairs as well. Reviewing the place of psychotherapy in the training of residents, the task force recommended an experience of 4 to 7 hours a week in the third year of training, with at least one patient seen more than once a week (17). Observing also that some schools are poorer in resources for teaching psychotherapy than others, it recommended at least 200 hours of total experience, one patient seen for more than 50 sessions, and some psychotherapy experience at at least weekly frequency for programs with limited resources.

It appears that the field has already anticipated these recommendations. If we assume a rough equivalence of programs and residents, the data from the present survey suggest that more than 60% of the psychiatrists now in training may complete their training without ever seeing a patient in twice-a-week or more intensive psychotherapy. Another 11% or so will have seen only one or two patients twice a week for any length of time. And if the Society for Psychotherapy Research reports are representative of current psychotherapy research, almost all research on outcomes and differences in outcome will be based on a model of psychotherapy once a week for 20 to 24 weeks, at the most.

Does it matter? Only if treatment more than one time a week is different as an experience, for both patient and therapist, and if more than once-a-week treatment for more than 24 weeks can yield results that are different from those producible in the current model.

Strangely enough, and despite much opinion on either side, we cannot yet answer these questions.

## REFERENCES

1. Romano J: On becoming a psychiatrist: 1934-1942. *JAMA* 1989; 261:2240-2242
2. American Medical Association: Essentials of accredited residencies, in *Directory of Graduate Medical Education Programs*. Chicago, AMA, 1989
3. Robinowitz CB, Kay J, Taintor Z (eds): *Directory of Psychiatry Residency Training Programs*, 4th ed. Washington, DC, American Psychiatric Press, 1988
4. Abstracts of the 19th Annual Meeting of the Society for Psychotherapy Research. Evanston, Ill, SPR, 1988
5. Grinspoon L, Ewalt J, Shader R: *Schizophrenia: Pharmacotherapy and Psychotherapy*. Baltimore, Williams & Wilkins, 1972
6. Jarrett RB, Rush AJ: Psychotherapeutic approaches for depression, in *Psychiatry*, vol 1. Edited by Cavenar JO Jr, Michels R, Brodie HKH, et al. Philadelphia, JB Lippincott, and New York, Basic Books, 1985
7. Klerman GL, Weissman MD, Rounsaville BJ, et al: *Interpersonal Psychotherapy of Depression*. New York, Basic Books, 1984
8. Rush AJ, Beck AT, Kovacs M, et al: Comparative efficacy of cognitive therapy and pharmacotherapy in the treatment of depressed outpatients. *Cognitive Therapy Research* 1977; 1:17-37
9. Eysenck HJ: The effects of psychotherapy. *Int J Psychiatry* 1965; 1:99-144
10. Williams JBW, Spitzer RL (eds): *Psychotherapy Research: Where Are We and Where Should We Go?* New York, Guilford Press, 1984
11. Tucker GJ: Psychotherapy will not be central in psychiatric education, in *Training Psychiatrists for the '90's*. Edited by Nadelson C, Robinowitz CB. Washington, DC, American Psychiatric Press, 1987
12. Smith M, Glass GV, Miller TI: *The Benefits of Psychotherapy*. Baltimore, Johns Hopkins University Press, 1980
13. Garfield SL, Bergin AE (eds): *Handbook of Psychotherapy and Behavior Change: An Empirical Analysis*, 3rd ed. New York, John Wiley & Sons, 1986
14. Klerman G: The *Osheroff* case: a rebuttal. *Psychiatr News*, April 7, 1989, pp 26, 27, 30
15. Eysenck HJ: The battle over psychotherapeutic effectiveness, in *Does Psychotherapy Really Help?* Edited by Hariman J. Springfield, Ill, Charles C Thomas, 1984
16. Tasman A, Kay J: Residency training in 1986, in *Training Psychiatrists for the '90's*. Edited by Nadelson C, Robinowitz CB. Washington, DC, American Psychiatric Press, 1987
17. Mohl PC, Lomax J, Tasman A, et al: Psychotherapy training for the psychiatrist of the future. *Am J Psychiatry* 1990; 147:7-13

# Spectrum of Efficacy of Valproate in 55 Patients With Rapid-Cycling Bipolar Disorder

Joseph R. Calabrese, M.D., and Gustavo A. Delucchi, M.D.

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*In order to explore valproate's spectrum of efficacy in rapid-cycling bipolar disorder, 55 patients underwent a prospective, open, 7.8-month trial designed to assess the drug's acute and prophylactic properties. Twenty patients received monotherapy, and 35 received combination therapy. Moderate to marked acute antidepressant responses were seen in 47% of the patients, prophylactic antidepressant responses in 76%, acute antimanic responses in 91%, prophylactic antimanic responses in 94%, acute responses in mixed states in 85%, and prophylactic responses in mixed states in 93%. Consistent with other anticonvulsant literature, these data suggest that valproate has marked antimanic and mixed state efficacy, but minimal to moderate antidepressant properties.*

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Although lithium therapy continues to be viewed as the treatment of choice for bipolar affective disorder, 20%–40% of patients either do not tolerate this drug or do not respond to it. A growing body of data suggests that rapid-cycling bipolar disorder accounts for a significant proportion of bipolar affective disorder that is resistant to lithium. Among bipolar patients, 13%–20% experience rapid cycling (1, 2). Since frequency of recurrence has previously been believed to contribute substantially to morbidity (3), improving the clinical management of this refractory patient population has the potential of significantly reducing human suffering. Such anticonvulsants as carbamazepine are believed to have particular efficacy in the management of rapid-cycling bipolar disorder (4). Although it has been demonstrated that carbamazepine has marked acute antimanic properties, its acute antidepressant properties are less impressive, and its prophylactic efficacy has recently been called into question (5, 6). The clinical use of carbamazepine is, in addition, compromised by its ability to induce its own metabolism, as well as to induce the metabolism of a variety of

different drugs (i.e., birth control pills, haloperidol, valproate) by enhancing the P-450 microsomal enzyme system (7, 8).

Although several authors have suggested valproate as an alternative to carbamazepine in the management of the patient with lithium-resistant rapid cycling, to our knowledge there have been no trials that have systematically studied large, homogeneous samples of patients with rapid-cycling bipolar disorder (9, 10). Since bipolar disorder is a recurrent illness accompanied by manic, depressed, and mixed states, the spectrum of efficacy in both the acute and prophylactic setting is of particular importance. Few studies have specifically evaluated the efficacy of valproate in these settings. Although this type of drug trial is more labor-intensive, the design may more accurately reflect pattern of response and long-term outcome in this complex, multifaceted, recurrent illness. In order to systematically explore valproate's spectrum of efficacy in the acute and prophylactic settings, patients with this refractory variant of bipolar disorder were prospectively given valproate either in monotherapy or combination therapy.

## METHOD

After giving informed consent, 55 patients who met *DSM-III-R* criteria for bipolar disorder were given a trial of valproate in a prospective, longitudinal, open design. These patients were consecutively referred to a bipolar disorder specialty clinic. In order to be included in the study, each patient was required to have a history of classic rapid cycling, as defined by Dunner and Fieve (1), i.e., a history of four or more major depressions, manias, or hypomanias per year. Consistent with *DSM-III-R*, patients with mixed states exhibited cycle frequencies too numerous to count and were further described as having discrete episodes of affective instability (mood lability) of such severity that the symptom complex of both hypomania and depression were present within the same 24-hour period. Before study entry, screening baseline thyroid function testing, CBC, and SMA-16 were done. Cycle frequency, duration, and severity were ascertained with life charting techniques and were confirmed by interviewing a family member. Patients were excluded

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Received June 14, 1989; revision received Oct. 2, 1989; accepted Oct. 31, 1989. From the Department of Psychiatry, University Hospitals of Cleveland, Case Western Reserve University. Address reprint requests to Dr. Calabrese, University Hospitals of Cleveland, Hanna Pavilion, 2040 Abington Rd., Cleveland, OH 44106.

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**TABLE 1. Characteristics of 55 Patients With Rapid-Cycling Bipolar Disorder**

Item	N	%
Women	32	58.1
Men	23	41.8
Physician-referred, previous treatment failures	38	69.1
Self-referred	17	30.9
Bipolar type I	25	45.5
Bipolar type II	30	54.5
Mixed states	14	25.5
Previously hospitalized	38	69.1
Unemployed due to illness	22	40.0
Overt thyroid failure	4	7.3
Family history of mood disturbance	41	74.5
Treatment failures		
Lithium alone	35	63.6
Carbamazepine alone	14	25.5
Lithium/carbamazepine combination	17	30.9
Current severe depressions <sup>a</sup>	49	89.1
Current severe manias <sup>a</sup>	27	49.1
Characteristics increasing since illness onset		
Number of cycles per year	46	83.6
Depression severity	32	58.2
Mania severity	26	47.3
Duration of depression	22	40.0
Duration of mania	16	29.1

<sup>a</sup>Patients were asked to rate the severity of their current mood states as mild, moderate, or severe.

from the study if they presented with elevated liver function test results or evidence of other CNS abnormalities. Valproate had never been previously prescribed for these patients. Previous bimodal therapy (lithium and carbamazepine) was classified as a failure if patients had experienced a major episode of depression, mania, or hypomania meeting *DSM-III-R* criteria or intolerable side effects.

Table 1 provides additional information for the total sample. The mean  $\pm$  SD age of the patients at entry to the study was  $40.7 \pm 13.4$  years; the mean age at onset of illness was  $19.3 \pm 11.2$  years. The mean number of cycles per year was  $9.2 \pm 9.7$  (median=6). The mean durations of the patients' current depressions and manias were  $46.0 \pm 68.0$  days and  $29.9 \pm 61.3$  days, respectively.

Outcome measures were defined as follows: marked improvement—complete cessation of all cycling (i.e., no breakthroughs of any kind); moderate improvement—improvement in cycle severity, duration, or frequency but with persistence of breakthrough mood swings; mild improvement; and no response. Valproate responders were defined as those patients who exhibited moderate or marked responses. Because this study assessed spectrum of efficacy in both acute and longitudinal settings, denominators describing outcome vary, since information concerning acute efficacy was obtainable only for those patients who presented with symptoms of the mood state in question. For example, if a patient presented depressed and responded

to valproate in acute and prophylactic settings, he or she would be likely to remain in complete remission. Since the prophylactic antimanic effects of a drug do not equal its acute effects, we cannot assume that successful prophylaxis against mania is equivalent to acute antimanic efficacy. This patient would never be available to test the acute antimanic properties of valproate. Therefore, sample sizes for prophylactic data sets were larger than those for acute efficacy data sets. Conversely, some patients who failed in a trial of valproate's acute effects were unable to participate in the prophylactic assessment; i.e., maintenance therapy could not be justified when acute responses were negligible. Anecdotal experience suggests that this chronically ill patient population commonly experiences substantial degrees of learned helplessness. As a result, interepisode psychosocial impairment remains after a complete response. For this reason, psychosocial function was not used as an outcome measure.

A regimen of divalproex sodium enteric-coated tablets was started at 250 mg b.i.d. and increased by 250 mg every 5–7 days, as tolerated. Valproate total levels, CBC, and repeat SMA-16 were obtained at baseline, 1 month, and 3 months during the first 6 months, and every 9–12 months thereafter. When valproate and carbamazepine were used together, free levels of each were monitored, since valproate is highly protein bound and noted to displace protein-bound carbamazepine.

In addition to receiving pharmacotherapy, study patients participated in a wide range of nonbiological interventions designed to obtain optimum compliance and assist in rehabilitation. These included rehabilitative psychotherapy, marital/family therapy, specialized outpatient manic-depressive groups for patients and families, and local involvement in the National Depressive and Manic Depressive Association. Alcoholics Anonymous, in vivo desensitization, and other behavioral interventions were used as indicated.

## RESULTS

Thirty-five of 55 patients (63.6%) were noted to be resistant to either lithium or carbamazepine. Twenty patients (36.4%) received valproate monotherapy and 35 (63.6%) combination therapy. Of the 35 who received combination therapy, 21 (60.0%) received valproate augmentation of lithium, five (14.3%) received unimodal antidepressants (e.g., tricyclic antidepressants, monoamine oxidase inhibitors), three (8.6%) valproate augmentation of lithium/carbamazepine therapy, and one (2.9%) valproate augmentation of carbamazepine. The mean  $\pm$  SD duration of this ongoing drug trial was  $7.8 \pm 5.9$  months (range=1–24, median=5.5 months). Patients had had evidence of illness for an average of 21.4 years. The mean valproate dose was  $1686 \pm 680$  mg; the mean serum level was  $84 \pm 28$   $\mu$ g/ml.

Table 2 describes analyses based on outcome criteria for both the entire sample of valproate-treated patients

**TABLE 2. Outcome of Patients With Rapid-Cycling Bipolar Disorder Who Received Valproate With or Without Other Drugs**

Mood State and Type of Treatment	Responders				
	Total	N	%	Marked Response N	% <sup>a</sup>
Total group (N=55)					
Mania					
Acute	34	31	91.2	19	61.3
Prophylactic	51	48	94.1	40	83.3
Depression					
Acute	34	16	47.1	13	81.3
Prophylactic	51	39	76.5	21	53.8
Mixed states					
Acute	14	12	85.7	12	100.0
Prophylactic	14	13	92.9	13	100.0
Patients who received valproate alone (N=20)					
Mania					
Acute	10	9	90.0	8	88.9
Prophylactic	20	19	95.0	17	89.5
Depression					
Acute	11	7	63.6	4	57.1
Prophylactic	20	17	85.0	11	64.7
Mixed states					
Acute	6	6	100.0	6	100.0
Prophylactic	6	6	100.0	6	100.0

<sup>a</sup>Based on number of responders.

and the 20 patients who received monotherapy. All three of the patients who did not respond to the acute antimanic properties of valproate had bipolar I rapid cycling. Of the patients with type I and II disorders, 84% (N=21) versus 93.3% (N=28) were responders in the acute setting; and 55.8% (N=14) versus 77.0% (N=23) exhibited marked responses. Comorbidity was prevalent, with 15 of 55 (27.3%) exhibiting state-dependent alcohol abuse, primary alcoholism in four (7.3%), other substance abuse in 12 (21.8%), panic attacks in 22 (40.0%), generalized anxiety in nine (16.4%), and obsessive-compulsive disorder in one (1.8%). Panic attacks subsided in 21 of 22 patients. State-dependent alcohol abuse remitted in 15 of 15 patients. Other substance abuse remitted in 12 of 12 patients. Dependence on alcohol unrelated to mood disturbance was treated with Alcoholics Anonymous in each of four patients; one of the four did not maintain sobriety. Non-state-dependent generalized anxiety remitted in eight of nine patients. Thyroid supplementation was continued in the four patients who had reported a previously treated hypothyroidism.

Twenty-nine of the 55 patients (52.7%) had side effects. There were eight reports of nausea, six of epigastric cramping, five of tremors, four of ataxia, four of lethargy, three of alopecia that was dose-related and resolved once the dose was decreased, and one each of slurred speech, blurred vision, rash, headache, enuresis, fluid retention, and hepatotoxicity. The drug was discontinued twice due to gastrointestinal upset, once due to alopecia, once due to de novo elevations of liver function test results, accompanied by signs of liver injury, in a patient

with acquired immune deficiency syndrome, and five times due to lack of antidepressant efficacy. The latter involved partial responders to lithium who had already experienced complete remission of their manias but were given valproate to treat residual major depression.

## DISCUSSION

Until recently, inadequate attention has been given to the spectrum of drug efficacy in the treatment of bipolar disorder. As the rapid-cycling variant of bipolar disorder becomes increasingly well-recognized, the spectrum of efficacy in both the acute and longitudinal settings will take on increasing importance. It is of particular concern to patients with the rapid-cycling variant. Before they are willing to relinquish their highs through effective antimanic therapy, many will query the physician as to the drug's antidepressant efficacy. They realize the currently available bimodal therapies are better antimanic agents than antidepressants. A unimodal assessment of an agent's antimanic properties in a placebo-controlled, double-blind setting is, therefore, complemented by longitudinal, naturalistic studies that individually assess manic, mixed, and depressed mood states in both the acute and prophylactic settings. Unfortunately, longitudinal, double-blind, placebo-controlled drug trials of this kind are expensive, critically reviewed by institutional review boards, and labor-intensive. Large sample sizes are required to accumulate adequate acute cohorts for the individual mood states, and study periods are lengthy. This prospective, open, longitudinal study of valproate monotherapy and combination therapy was designed to address some of these concerns.

Consistent with other anticonvulsant literature, our data suggest that valproate possesses potent antimanic and mixed state properties in both the acute and prophylactic settings but minimal to moderate antidepressant properties. The frequency of prior psychiatric hospitalizations, resistance to lithium/carbamazepine treatment, bipolar type I disease, and unemployment suggest that these patients were quite ill and did not have merely less serious variants of mood disturbance, such as cyclothymia. Patients' reports with respect to years since onset of illness (21.4) and duration and severity of illness also suggested significant levels of impairment (see table 1). Of particular interest is the observation that 84% of the patients reported that their disease became more autonomous as it "matured." They noted that the cycles became more frequent and had no apparent relationship to any stressful life event. This feature, in particular, has been viewed in the past as a predictor of poor outcome. Approximately half viewed the amplitude of their manias and depressions as increasing. Nearly half reported increased durations of depressions over the course of their illness, and over one-fourth reported increased durations of manias.

Due to the ambiguity of our *DSM-III-R* criteria for



mixed states, the data concerning valproate's marked efficacy in mixed states in our sample of 14 patients must be viewed with caution. As the mean duration of these mixed states was  $18.7 \pm 23.9$  days (range=1–70 days), these episodes were not just short transitional states as frequently seen when patients cycle from a high to a low or vice versa. These subjects cycled into mixed states that persisted for substantial periods of time and exhibited the best outcome. In fact, some would specify that these patients be more accurately referred to as ultrafast rapid cyclers, i.e., having cycles of less than 48 hours (11). Since in most cases their cycle frequencies were too numerous to count, we elected to stay within the *DSM-III-R* criteria. Our findings for this mood state, however, are consistent with the literature, which suggests that anticonvulsants are particularly helpful in the management of mixed states (12).

Of particular note is valproate's marked antimanic efficacy in this otherwise refractory patient population. Although the antidepressant properties of this drug were clear-cut, they were less impressive and again suggest that we have yet another bimodal agent with minimal to moderate antidepressant efficacy. For this reason, the challenge of treating the depressed phase of rapid-cycling bipolar disorder persists. Should conventional unimodal antidepressants be used and risk exacerbating cycle frequency (13), or should bimodal therapies (i.e., lithium, carbamazepine, valproate) be relied on solely? Future drug trials might be directed toward the development of well-tolerated bimodal pharmacotherapies that possess potent antidepressant properties. In addition, a self-administered rating scale is needed that can be given both serially and prospectively to this outpatient population and used to quan-

tify cycle frequency, severity, and duration. Such an instrument is currently under development and will assist in the systematic evaluation of the periodic phenomena of rapid-cycling in affective disorders.

## REFERENCES

1. Dunner DL, Fieve RR: Clinical factors in lithium prophylaxis failure. *Arch Gen Psychiatry* 1974; 30:229–233
2. Dunner DL, Patrick D, Stallone F, et al: Rapid-cycling manic depressive patients. *Compr Psychiatry* 1977; 18:561–565
3. Kukopulos A, Reginaldi D, Laddomada P, et al: Course of the manic-depressive cycle and changes caused by treatment. *Pharmacopsychiatry* 1980; 13:156–167
4. Post RM, Uhde TW, Ballenger JC, et al: Prophylactic efficacy of carbamazepine in manic-depressive illness. *Am J Psychiatry* 1983; 140:1602–1604
5. Frankenburg FR, Tohen M, Cohen BM, et al: Long-term response to carbamazepine: a retrospective study. *J Clin Psychopharmacol* 1988; 8:130–132
6. Prien RF, Gelenberg AJ: Alternatives to lithium for preventive treatment of bipolar disorder. *Am J Psychiatry* 1989; 146:840–848
7. Mikati MA, Browne TR, Collins JF: Time course of carbamazepine autoinduction. *Neurology* 1989; 39:592–594
8. Hansten PD, Horn JR: Inhibition of oral contraceptive efficacy. *Drug Interactions Newsletter* 1985; 5:7–10
9. McElroy SL, Keck PE, Pope HG, et al: Valproate in the treatment of rapid-cycling bipolar disorder. *J Clin Psychopharmacol* 1988; 8:275–279
10. Calabrese JR, Delucchi G: Phenomenology of rapid-cycling manic depression and its treatment with valproate. *J Clin Psychiatry* 1989; 50:30–34
11. Alarcon R: Rapid-cycling affective disorders: a clinical review. *Compr Psychiatry* 1985; 26:522–540
12. Himmelhoch JM, Garfinkel ME: Mixed mania: diagnosis and treatment. *Psychopharmacol Bull* 1986; 22:613–620
13. Wehr TA, Goodwin FK: Rapid cycling in manic depressives induced by tricyclic antidepressants. *Arch Gen Psychiatry* 1979; 36:555–559

# Progression of Illness in the Differential Diagnosis of Primary Dementia

George S. Zubenko, M.D., Ph.D.

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*The diagnostic utility of determinations of insidious or stepwise progression of illness was examined in 124 geriatric inpatients with primary dementia. Such determinations failed to distinguish patients with primary degenerative dementia of the Alzheimer type from those with multi-infarct dementia. Episodic behavioral complications, especially depression and delusions, in the patients with primary degenerative dementia were associated with stepwise progression. Determinations of stepwise progression were made in only six (15%) of the 40 demented patients with at least two cerebral infarctions, a finding inconsistent with current diagnostic criteria for multi-infarct dementia.*

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Prospective clinical data describing the onset of illness or its progression are rarely available for patients who present for the initial evaluation and treatment of dementia. However, both of these clinical determinations are used in the classification of this group of disorders according to *DSM-III*, *DSM-III-R*, and the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (1). Using these variables in the differential diagnosis of dementia requires that assessments of age at symptom onset and of progression of illness be made in retrospect on the basis of available historical information obtained from family members, caregivers, treating physicians, and previous medical records.

A considerable body of evidence from clinical (2-5), family (6-8), and genetic (9-11) studies and from bio-

chemical and neuropathologic studies of brain (12-15) and other tissues (8, 11, 16, 17) supports the importance of including age at onset in the description of this disorder. However, the value of characterizations of the progression of illness in the differential diagnosis of primary dementia has seldom been studied empirically (18, 19), especially in psychiatric settings, where behavioral symptoms are common reasons for referral. In the current study, I examined the utility of assessments of insidious or stepwise progression of illness in the differential diagnosis of 124 geriatric inpatients with primary degenerative dementia of the Alzheimer type or multi-infarct dementia.

## METHOD

The study sample was selected from 575 inpatients over the age of 55 years who were admitted to the Geriatric Health Services at Western Psychiatric Institute and Clinic during 1987. Fourteen repeat admissions during this interval were excluded. Geriatric Health Services provides primary outpatient, inpatient, and nursing care services to elders in Allegheny County, Pa. In addition, it provides specialty services for patients referred from other hospitals of the Health Center of the University of Pittsburgh and serves as a tertiary referral center for community hospitals and nursing homes in the tristate area. Reasons for referral of patients to the inpatient component of Geriatric Health Services typically involve the emergence of behavioral dysfunction due to mental disorders of late life.

A complete history was taken, and each patient underwent physical, neurologic, psychiatric, and detailed mental status examinations. Other tests included a CBC, urinalysis, blood chemistry screen, thyroid function tests, serology, measurement of serum folate and B<sub>12</sub> levels and blood levels of prescribed medications, chest X-ray, ECG, EEG, and brain imaging by means of either computerized tomography (CT) or magnetic resonance imaging (MRI), as indicated. Patients who met the *DSM-III-R* criteria for primary degenerative dementia of the Alzheimer type or multi-infarct dementia except for a stepwise deterioration and who had received MRI or CT scans of the head while hospitalized were included in the study. This last criterion

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Received April 11, 1989; revision received Aug. 30, 1989; accepted Sept. 18, 1989. From the Geriatric Health Services, Department of Psychiatry, University of Pittsburgh and Western Psychiatric Institute and Clinic. Address reprint requests to Dr. Zubenko, Western Psychiatric Institute and Clinic, Rm. E-1230, 3811 O'Hara St., Pittsburgh, PA 15213.

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TABLE 1. Sex, Age, and Progression of Illness in 124 Geriatric Inpatients With Primary Degenerative or Multi-Infarct Dementia

Diagnosis	N	Sex		Age (years)		Type of Progression					
						Insidious		Stepwise		Uncertain	
		M	F	Mean	SD	N	%	N	%	N	%
Primary degenerative dementia,											
Alzheimer type	84 <sup>a</sup>	20	64	75.5	9.2	60	71	9	11	15	18
Uncomplicated	43	10	33	76.6	10.6	35	82 <sup>b</sup>	2	5	6	14
Complicated <sup>c</sup>	41	10	31	74.3	7.3	25	61 <sup>b</sup>	7	17	9	22
Delusions	21	—	—	—	—	14	45	3	10	4	13
Depression	16	—	—	—	—	9	56	4	25	3	19
Delirium	4	—	—	—	—	2	50	0	0	2	50
Multi-infarct dementia	40	8	32	78.1	8.0	22	55	6	15	12	30
Uncomplicated	26	6	20	79.3	7.7	14	54	6	23	6	23
Complicated <sup>c</sup>	14	2	12	75.9	8.4	8	57	0	0	6	43

<sup>a</sup>Includes six patients with onset before age 65.

<sup>b</sup>Significant difference between patients with (25 of 41) and without (35 of 43) behavioral complications ( $\chi^2=4.29$ ,  $df=1$ ,  $p<0.05$ ).

<sup>c</sup>Refers to presence of behavioral complications (delusions, depression, or delirium), as described in *DSM-III-R*.

was employed so that the clinical and radiologic assessments would be contemporaneous. All subjects who met the *DSM-III-R* criteria for primary degenerative dementia of the Alzheimer type also met the NINCDS-ADRDA consensus criteria for probable or possible Alzheimer's disease. Since the clinical diagnostic criteria for multi-infarct dementia have not been operationalized in *DSM-III-R*, evidence of at least two independent cerebrovascular accidents as determined by neurologic examination and brain imaging was required for the establishment of this diagnosis. The diagnostic criteria were applied by interdisciplinary treatment teams that included Board-certified psychiatrists and internists, nurses, social workers, and occupational therapists, all with expertise in geriatrics. Of the 575 independent patients admitted during 1987, 115 (20%) met the diagnostic criteria for primary degenerative dementia of the Alzheimer type, 46 (8%) met the criteria for multi-infarct dementia, and 23 (4%) had dementias of other suspected etiology or mixed etiologies. A total of 84 patients with primary degenerative dementia of the Alzheimer type (presenile onset,  $N=6$ ; senile onset,  $N=78$ ) and 40 with multi-infarct dementia met the selection criteria for this study.

Characterization of the progression of each patient's impairment as "insidious and generally progressive" or "stepwise" was performed by a single Board-certified psychiatrist with expertise in geriatric psychiatry. This determination was based on clinical descriptions provided by caregivers and family members as part of a semistructured diagnostic interview (20), the social history obtained by qualified geriatric social workers, reports from referring physicians, and medical records. This process was made as systematic as possible in the context of a thorough clinical evaluation. The rater was blinded to the medical history, review of systems, and the results of the physical and neurologic examinations, brain imaging, and laboratory tests. On the basis of the information available to the rater, determinations of insidious or stepwise progression could

be made in 97 (78%) of the 124 cases included in this study. The reliability of these determinations was acceptable: for a subset of 34 randomly chosen cases (20 insidious, nine stepwise, and five uncertain), 29 (85%) were reassigned the same progression types.

The mean ages and the sex ratios of the groups with primary degenerative dementia of the Alzheimer type and multi-infarct dementia were compared with a two-tailed *t* test and chi-square statistic, respectively. Logistic regression analysis was used to evaluate the significance of the clinical assessments of progression of illness in predicting whether demented patients would exhibit clinical and/or neuroradiologic evidence of multi-infarct dementia, while controlling for age and gender. The hypothesis that the emergence of behavioral complications (delusions, depression, delirium) in primary degenerative dementia was less likely to be associated with insidious progression was tested by comparing the prevalence rates of insidious progression among the patients with and without these complications by means of chi-square analysis.

## RESULTS

The characteristics of the 124 geriatric inpatients with progressive primary dementia who were included in this study are presented in table 1. Primary degenerative dementia of the Alzheimer type was 2.1 times as prevalent as multi-infarct dementia, a ratio similar to the ratio of 2.5 (115 to 46) for all 1987 admissions to the inpatient service, from which the study sample was drawn. Patients with presenile onsets (before age 65) represented a small proportion (six of 84, 7%) of those hospitalized with primary degenerative dementia, consistent with previous estimates of the age-specific incidence of Alzheimer's disease (6, 21). The study groups with primary degenerative dementia of the Alzheimer type and multi-infarct dementia were similar in mean age ( $t=1.56$ ,  $df=122$ , *n.s.*) and sex ratio ( $\chi^2=0.22$ ,  $df=1$ , *n.s.*) (see table 1).

The focus of the current study was to test the usefulness of determinations of the progression of illness as insidious or stepwise in the differential diagnosis of primary dementia (table 1). Overall, 82 (66%) of the 124 patients were determined to have had insidious deteriorations, 15 (12%) had stepwise courses, and a determination of either insidious or stepwise could not be made in the remaining 27 (22%) cases. In fact, an insidious course was the most common presentation of primary dementia regardless of the etiology of the dementia. Logistic regression was used to evaluate the significance of the clinical characterizations of progression of illness in differentiating patients with primary degenerative dementia from those with multi-infarct dementia, while controlling for age and gender. The assessments of progression of illness ( $\chi^2=3.06$ ,  $df=2$ ,  $p=0.22$ ) were not useful in this regard, nor was age ( $\chi^2=2.47$ ,  $df=1$ ,  $p=0.12$ ) or gender ( $\chi^2=0.13$ ,  $df=1$ ,  $p=0.72$ ) significantly associated with clinical and/or neuroradiologic evidence of multiple cerebral infarctions.

The emergence of behavioral complications was an important determinant of whether the progression of primary degenerative dementia was characterized as insidious or stepwise (table 1). Among the patients with primary degenerative dementia, those with delusions, depression, or delirium had a significantly lower prevalence of insidious progression than the patients without these complications ( $\chi^2=4.29$   $df=1$ ,  $p<0.05$ ).

## DISCUSSION

The first issue addressed by this study was the feasibility of establishing whether the progression of dementia was insidious or stepwise on the basis of multiple sources of information; such determinations were possible in 97 (78%) of the 124 cases. For the cases in which assignment to one of these two classifications could not be made, the fluctuations in the course of the illness were sufficiently prominent to preclude its description as insidious but not so large as to be clearly stepwise without return to previous levels of functioning. In no case did the classification of progression as "uncertain" derive from an unresolvable conflict in the descriptions of the course from separate sources of information.

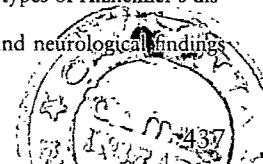
The principal finding of this study was that determinations of the progression of illness did not distinguish patients with primary degenerative dementia of the Alzheimer type from those with multi-infarct dementia. Within the group of patients with primary degenerative dementia, the emergence of episodic behavioral complications, especially depression and delusions, contributed significantly to the interpretation of the course of illness as stepwise or uncertain. Furthermore, the coexistence of occult cerebrovascular disease, undetected by ratings of neurologic signs and symptoms, EEG, and brain imaging, may have also contributed to the classification of at least some of these cases as step-

wise or uncertain (19, 22–26). While there are at least two explanations for the cases of stepwise progression among a fraction of the patients with primary degenerative dementia, the observation that only 15% (six of 40) of the patients with multi-infarct dementia had clear evidence of stepwise progression is not consistent with current diagnostic formulations of multi-infarct dementia, including those in *DSM-III* and *DSM-III-R*.

It should be noted that the emergence of significant behavioral changes or syndromes, rather than cognitive decline per se, constitutes the primary reason for the referral of patients with dementia to our inpatient psychiatric setting. This factor and our mission as a tertiary care facility are likely to be important sources of referral bias, so these findings may not generalize to other clinical settings or to unselected populations. Nonetheless, the results of this study have led us to de-emphasize assessments of the course of illness in the differential diagnosis of progressive primary dementia and to rely more heavily on focal neurologic signs and symptoms and on neuroradiologic evidence to distinguish primary degenerative from vascular dementias.

## REFERENCES

1. McKhann G, Drachman D, Folstein M, et al: Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984; 34:939–944
2. Kaszniak AW, Fox J, Gandell DL, et al: Predictions of mortality in presenile and senile dementia. *Ann Neurol* 1978; 3:246–252
3. Seltzer B, Sherwin I: A comparison of clinical features in early- and late-onset primary degenerative dementia. *Arch Neurol* 1983; 40:143–146
4. Filley CM, Kelly J, Heaton RK: Neuropsychologic features of early- and late-onset Alzheimer's disease. *Arch Neurol* 1986; 43:574–576
5. Becker JT, Huff FJ, Nebes RD, et al: Neuropsychological function in Alzheimer's disease: patterns of impairment and rates of progression. *Arch Neurol* 1988; 45:263–268
6. Breitner JCS, Folstein MF, Murphy EA: Familial aggregation in Alzheimer dementia, I: a model for the age-dependent expression of an autosomal dominant gene. *J Psychiatr Res* 1986; 20:31–43
7. Huff FJ, Auerbach J, Chakravarti A, et al: Risk of dementia in relatives of patients with Alzheimer's disease. *Neurology* 1988; 38:786–790
8. Zubenko GS, Huff FJ, Beyer J, et al: Familial risk of dementia associated with a biologic subtype of Alzheimer's disease. *Arch Gen Psychiatry* 1988; 45:889–893
9. St George-Hyslop PH, Tanzi RE, Polinsky RJ, et al: The genetic defect causing familial Alzheimer's disease maps on chromosome 21. *Science* 1987; 235:885–890
10. Goate AM, Owen MJ, James LA, et al: Predisposing locus for Alzheimer's disease on chromosome 21. *Lancet* 1989; 1:352–355
11. Chakravarti A, Slaugenhaupt SA, Zubenko GS: Inheritance pattern of platelet membrane fluidity in Alzheimer disease. *Am J Hum Genet* 1989; 44:799–805
12. Bird TD, Stranahan S, Sumi SM, et al: Alzheimer's disease: choline acetyltransferase activity in brain tissue from clinical and pathological subgroups. *Ann Neurol* 1983; 14:284–293
13. Rossor MN, Iverson LL, Reynolds GP, et al: Neurochemical characteristics of early- and late-onset types of Alzheimer's disease. *Br Med J* 1984; 288:961–964
14. Roth M: The association of clinical and neurological findings





# Dysfunctional Attitudes in Depressed Patients Before and After Clinical Treatment and in Normal Control Subjects

Eric D. Peselow, M.D., Clive Robins, Ph.D., Paul Block, Ph.D.,  
Faouzia Barouche, M.D., and Ronald R. Fieve, M.D.

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*To evaluate the role of maladaptive thinking patterns in depression, the authors administered the Dysfunctional Attitude Scale to 112 depressed patients before and after 3–6 weeks of treatment with antidepressants or placebo. Twenty-two normal subjects were also assessed twice. Depressed patients had a significantly higher initial mean score than control subjects, but during treatment their score significantly decreased, and the posttreatment score of those with complete recoveries was nearly as low as the control subjects' final score. The higher the initial dysfunctional attitude score the poorer the response to treatment. Patients with endogenous depression had significantly lower scores than nonendogenously depressed patients.*

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Depressive symptoms include dysphoria, anhedonia, weight loss, self-deprecation, hopelessness, feelings of worthlessness, sleep disturbance, and lethargy. The cognitive approach to understanding and treating depression is based on the premise that in addition to these symptoms, persistent negative cognitions are an essential component of depression. Rush and Beck (1) have hypothesized that these maladaptive thinking patterns or dysfunctional attitudes are related to the onset and maintenance of clinical depression.

Weissman (2) developed the Dysfunctional Attitude Scale to measure maladaptive thinking patterns or schemata, which, according to Beck's cognitive theory,

are relatively stable characteristics predisposing individuals to depression (3). However, contrary to this theory is the school of thought which holds that dysfunctional attitudes are primarily concomitants of the depressive state which decrease as the patient recovers from depression (4–7).

It may be that some depressions are characterized by dysfunctional attitudes (5) and that these depressions may be less likely to respond to somatic treatments and more likely to respond to other treatment modalities, such as cognitive therapy. Similarly, dysfunctional attitudes may be more associated with nonendogenous than endogenous depression.

To test these hypotheses, we evaluated the Dysfunctional Attitude Scale scores of depressed outpatients before and 3–6 weeks after they entered one of three double-blind, placebo-controlled outpatient antidepressant medication trials and compared these scores with the scores of normal control subjects who were tested twice at comparable times. The purpose of this study was fourfold: 1) to compare the Dysfunctional Attitude Scale scores of the depressed patients and the normal subjects, 2) to compare the changes in scores of the drug and placebo responders with those of the drug and placebo nonresponders, 3) to determine whether initial dysfunctional attitude score helps predict response to drug or placebo, and 4) to compare the scores of patients with endogenous and nonendogenous depression before and after treatment.

## METHOD

Over the past 4 years, our group has conducted three outpatient drug studies. Two of these were comparisons of the antidepressant fluoxetine and placebo (range of fluoxetine doses=20–60 mg/day and 5–40 mg/day, respectively) and one was a comparison of clovoxamine hydrochloride (50–350 mg/day), imipramine hydrochloride (70–245 mg/day), and placebo. The patients were randomly assigned to treatment groups; for both fluoxetine studies there was a 3:1 drug-placebo ratio, and for the clovoxamine study the ratio of patients receiving clovoxamine, imipramine, and placebo was 1:1:1. All patients who participated in these three trials gave voluntary informed consent to

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Received Oct. 26, 1988; revisions received May 1 and Aug. 30, 1989; accepted Oct. 12, 1989. From the Department of Psychology and the Department of Psychiatry, School of Medicine, New York University, New York; the Department of Psychiatry, Duke University School of Medicine, Durham, N.C.; the Foundation for Depression and Manic Depression, New York; and the Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York. Address reprint requests to Dr. Peselow, 1322 East 84th St., Brooklyn, NY 11236.

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do so. All patients involved in these trials were between 18 and 65 years of age, met the *DSM-III* criteria for major depression, and had scores of 16 or higher on the Hamilton depression scale (8). If a patient fulfilled the entry criteria for any of the three studies, he or she was given placebo in a single-blind fashion over 4–10 days. All patients were rated with the Hamilton depression scale, the 21-item Beck Depression Inventory (9), the Clinical Global Impression (CGI) (10), the 3-point Raskin depression scale (11), and an endogenous symptom scale abstracted from the Schedule for Affective Disorders and Schizophrenia, Change Version (SADS-C) (12). In addition, a determination was made as to whether the patient did or did not meet the Research Diagnostic Criteria (RDC) for definite endogenous depression (13).

During this period of single-blind placebo administration the patients received various assessments, which have been described elsewhere (14). One of the assessments was the Dysfunctional Attitude Scale (2), which is a self-rated 40-item questionnaire in which each item is measured on a scale of 1–7 (range of possible scores=40–280). It assesses such dysfunctional thoughts as concerns about the attitudes of others, fixed negative views about the world, and perfectionistic goals. Each subject was placed in an office and completed the scale alone after the questionnaire was explained. The Dysfunctional Attitude Scale has been shown to have an alpha coefficient of 0.90 or better (5, 15).

The patient was reassessed with the same rating scales after the 4–10-day period. If the patient's Hamilton score did not drop more than 20% and remained 16 or higher, the patient was able to enter one of the three drug trials. All three studies involved 6-week trials of active drug (fluoxetine, imipramine, clovoxamine) or placebo. Drug treatment was the only modality used; the trials did not involve any psychotherapeutic modality. The patients were seen weekly and rated with the same scales. At the end of the 6-week course or at the final analysis (between 3 and 6 weeks), a determination of response to treatment was made. A response to treatment was defined as a reduction in both the Hamilton and Beck scores of 50% or more and a final Hamilton score of 11 or less. At the conclusion of the trials we administered the Dysfunctional Attitude Scale to as many patients as possible.

Overall, 157 patients entered the double-blind phases of the three studies. We were able to obtain pre- and posttreatment scores on the Dysfunctional Attitude Scale for 112 of them (71.3%). After the conclusion of these trials we administered the Dysfunctional Attitude Scale to 22 individuals with no lifetime history of affective disorder and no lifetime history of pharmacological treatment for psychiatric illness; these normal control subjects were assessed at the beginning and end of a comparable time period (3–6 weeks). In both cases, the 40-item B form was used. There was no difference in initial clinical status, as measured with the Hamilton, Raskin, and CGI scales,

between the 45 patients in the drug trials who did not complete the Dysfunctional Attitude Scale at both times and the 112 who participated in our evaluation.

For the purposes of the analysis, we combined the imipramine, fluoxetine, and clovoxamine groups into a single antidepressant group. Our justification for this is evidence in the literature suggesting that fluoxetine (16) and clovoxamine (17) are equal in antidepressant efficacy to standard agents, such as imipramine (since this evaluation, fluoxetine has been approved by the U.S. Food and Drug Administration for major depression). We then split the drug and placebo groups into drug responders and nonresponders and placebo responders and nonresponders to see if there were differences.

## RESULTS

When the code was broken, it was found that 77 of the patients had been randomly assigned to drug (fluoxetine, clovoxamine, or imipramine) and 35 patients had been assigned to placebo. Of the 77 patients assigned to drug, 41 (53.2%) were classified as responders according to our criteria, whereas only 11 (31.4%) of the 35 patients assigned to placebo were responders. This difference was statistically significant ( $\chi^2=3.86$ ,  $df=1$ ,  $p<0.05$ , with Yates' correction factor).

The overall approach to the data analysis was analysis of variance (ANOVA). The between-subjects variables were diagnosis, drug status, and subtype (responder or nonresponder, endogenous or nonendogenous). The rating time (baseline or after treatment for the patients and first or second rating for the control subjects) was treated as a within-subject repeated factor. All pairwise comparisons and contrasts were considered significant if the significance level was  $p<0.05$ .

Table 1 shows the difference in initial clinical status between both placebo and drug responders and nonresponders. Using a two-factor ANOVA (response and drug status), we found no difference in initial scores on the Hamilton scale, CGI, endogenous symptom scale, and Raskin scale between responders and nonresponders for either the placebo or drug group (most  $F$  ratios  $<1$ ). However, on the Beck scale there was a main effect for response ( $F=4.45$ ,  $df=1$ , 108,  $p=0.04$ ) due to higher scores for the nonresponders, which was most pronounced for the drug-treated group, in which the nonresponders had a significantly higher initial mean Beck score than the responders. However, neither the main effect for drug status ( $F<1$ ,  $df=1$ , 108) nor the interaction between drug status and response ( $F=1.50$ ,  $df=1$ , 108) reached significance.

The initial scores on the Dysfunctional Attitude Scale (mean  $\pm$  SD) for the 112 depressed patients and 22 control subjects were  $151.41 \pm 35.3$  and  $99.46 \pm 22.7$ , respectively. Their scores 3–6 weeks after treatment were  $139.21 \pm 41.4$  and  $96.05 \pm 22.9$ , respectively. Using one between-subjects factor (diagnosis) and one within-subject factor (time of rating) in a re-



**TABLE 1. Initial Clinical Status of Responding and Nonresponding Depressed Patients Given Drug or Placebo**

Group	Initial Score									
	Hamilton Depression Scale		Beck Depression Inventory		Raskin Depression Scale		Clinical Global Impression		Endogenous Symptom Scale	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Drug										
Responders (N=41)	23.73	4.5	24.39 <sup>a</sup>	6.9	9.68	1.3	4.17	0.7	33.07	7.1
Nonresponders (N=36)	23.86	5.4	29.61 <sup>a</sup>	7.9	10.19	1.9	4.25	0.8	33.61	6.5
Placebo										
Responders (N=11)	25.09	4.5	25.36	6.4	9.91	1.5	4.36	0.7	33.82	7.0
Nonresponders (N=24)	25.33	5.1	26.75	7.4	10.67	2.0	4.50	0.8	35.25	7.4

<sup>a</sup>According to a two-way ANOVA (Response by Drug Status), there was a significant main effect of response for the Beck score ( $F=4.45$ ,  $df=1, 108$ ,  $p<0.04$ ) and a statistically significant difference between drug responders and nonresponders ( $t=2.31$ ,  $df=75$ ,  $p<0.05$ ).

peated measure ANOVA, we found a statistically significant Diagnosis by Time interaction ( $F=4.80$ ,  $df=1, 132$ ,  $p<0.03$ ). Pairwise comparisons showed that the depressed patients endorsed significantly more dysfunctional attitudes both before and after treatment than did the control subjects ( $t=5.04$ ,  $df=132$ ,  $p<0.0001$ , and  $t=4.19$ ,  $df=132$ ,  $p<0.0001$ , respectively). For both groups, the dysfunctional attitude score decreased between the first and second assessments, but the decrease was greater for the depressed group ( $t=3.93$ ,  $df=132$ ,  $p<0.001$ ). The Dysfunctional Attitude Scale scores of our depressed and control subjects were similar to those in other reports (4, 5).

Table 2 contains the Dysfunctional Attitude Scale scores before and after treatment of the patients who subsequently responded or did not respond to drug or placebo. Before treatment, the mean scores did not differ between the 77 patients assigned to drug and the 35 patients assigned to placebo ( $t=1.59$ ,  $df=110$ , n.s., two-tailed). Using two between-groups variables (drug status and response) and one within-subject variable (time of rating) in a repeated measures ANOVA, we noted a Response by Drug Status by Time interaction ( $F=8.94$ ,  $df=1, 108$ ,  $p=0.003$ ). Pairwise comparisons indicated numerous important statistically significant differences between groups. In the drug-treated group, the responders had a significantly lower initial mean score than the nonresponders. In the placebo group, the responders had a lower initial score than the nonresponders, but the difference just missed statistical significance. In both the drug and placebo groups, the responders showed a significantly greater decrease in score after treatment than the nonresponders, who showed virtually no change in dysfunctional attitude score after treatment.

Figure 1 compares the pre- and posttreatment scores of all responders, all nonresponders, and the control subjects. Using one between-subjects variable (group) and one within-subject variable (time of rating) in an ANOVA, we found a significant Group by Time interaction ( $F=41.96$ ,  $df=2, 131$ ,  $p<0.0001$ ). Pairwise comparisons indicated that for both the pre- and posttreatment ratings the responders had significantly lower mean scores than the nonresponders. However,

the control subjects had significantly lower ratings than both the responders and nonresponders at both ratings. Thus, despite the fact that the dysfunctional attitude score of the combined drug and placebo responders significantly decreased, responders continued to endorse more dysfunctional attitudes than control subjects tested a second time.

Of the 112 patients, 65 (58%) met the RDC for definite endogenous depression, and 47 (42%) did not and were classified as having nonendogenous depression. In the drug-treated group, 19 (44%) of the 43 patients with endogenous depression and 22 (65%) of the 34 patients with nonendogenous depression responded to treatment ( $\chi^2=2.45$ ,  $df=1$ ,  $p>0.1$ , with Yates' correction factor). In the placebo group, response occurred in five (23%) of the 22 patients with endogenous depression and six (46%) of the 13 patients with nonendogenous depression ( $\chi^2=1.13$ ,  $df=1$ ,  $p>0.25$ , with Yates' correction factor).

Table 3 contains the Dysfunctional Attitude Scale scores of the patients with endogenous and nonendogenous depression and the control subjects. Using one between-subjects factor (group) and one within-subject factor (time of rating) in the ANOVA, we found a significant Group by Time interaction ( $F=3.66$ ,  $df=2, 131$ ,  $p<0.03$ ). Important pairwise comparisons showed that the patients classified as having endogenous depression had significantly lower initial and posttreatment dysfunctional attitude scores than the group with nonendogenous depression. This was true for patients assigned to both drug and placebo. However, the endogenous group still had significantly higher initial and posttreatment scores than the normal control subjects. For both the endogenous and nonendogenous groups, the higher the initial score the poorer the response to drug or placebo ( $F=11.48$ ,  $df=3, 108$ ,  $p<0.0001$ ). Among the patients with endogenous depression, there was a significant difference in initial score on the Dysfunctional Attitude Scale between the responders ( $125.7\pm24.1$ ) and nonresponders ( $153.1\pm31.2$ ) ( $t=3.43$ ,  $df=63$ ,  $p<0.002$ ). The same was true for the responders and nonresponders in the nonendogenous group ( $150.4\pm36.0$  versus  $181.7\pm31.3$ ;  $t=3.38$ ,  $df=45$ ,  $p<0.002$ ).

**TABLE 2. Pre- and Posttreatment Scores on the Dysfunctional Attitude Scale of Responding and Nonresponding Depressed Patients Given Drug or Placebo**

Group	Score on Dysfunctional Attitude Scale <sup>a</sup>					
	Before Treatment <sup>b</sup>		After Treatment <sup>c</sup>		Change <sup>d</sup>	
	Mean	SD	Mean	SD	Mean	SD
Drug						
Responders (N=41)	140.29	30.7	111.80	29.7	-28.49	16.5
Nonresponders (N=36)	171.47	32.2	172.19	32.7	+0.72	18.8
Placebo						
Responders (N=11)	134.09	42.0	119.27	41.8	-14.82	7.0
Nonresponders (N=24)	148.25	31.6	145.70	32.7	-2.45	11.5

<sup>a</sup>Significant Drug Status by Response by Time interaction ( $F=8.94$ ,  $df=1, 108$ ,  $p=0.003$ ).

<sup>b</sup>Significantly lower score for drug responders than drug nonresponders ( $t=3.04$ ,  $df=75$ ,  $p<0.005$ ) and a trend in that direction for the placebo group ( $t=1.78$ ,  $df=33$ ,  $p=0.07$ ).

<sup>c</sup>Significantly lower score in responders than in nonresponders for both the drug group ( $t=5.92$ ,  $df=75$ ,  $p<0.0001$ ) and placebo group ( $t=2.56$ ,  $df=33$ ,  $p<0.02$ ).

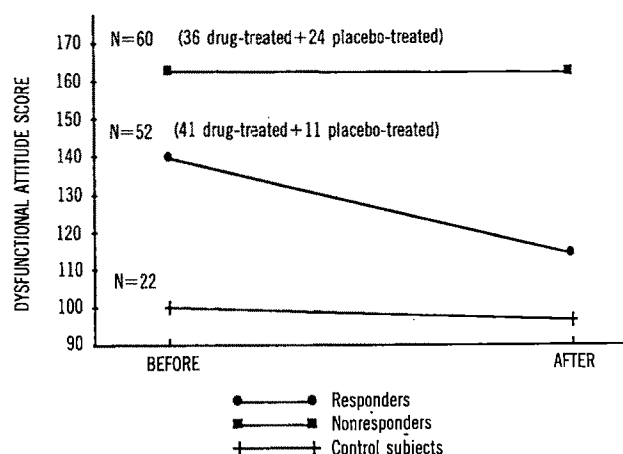
<sup>d</sup>Significantly greater decrease in responders than in nonresponders for both the drug group ( $t=13.48$ ,  $df=75$ ,  $p<0.0001$ ) and placebo group ( $t=3.59$ ,  $df=33$ ,  $p<0.005$ ).

## DISCUSSION

The findings reported here agree with those of Miranda and Persons (18) in that dysfunctional attitudes were mood dependent, as shown by the fact that alleviation of depression (by either drug or placebo) significantly lowered the Dysfunctional Attitude Scale score. This relationship has also been shown by other investigators (5–7, 19–22). The finding of a difference in dysfunctional attitudes between recovered depressed patients and control subjects agrees with that of Eaves and Rush (4) but not with other results (7, 21, 22). This interesting finding has two possible explanations. One is that dysfunctional attitudes may be trait-related; Miranda and Persons (18) noted that individuals with current depressive symptoms and histories of depressive episodes had higher Dysfunctional Attitude Scale scores than individuals with current depressive symptoms but no history of actual depressive episodes.

However, there is another possible explanation for this difference. It might be that although our patients met generally accepted criteria for response to treatment, this response might not be consistent with complete recovery. (Average final Hamilton scores for the 41 drug and 11 placebo responders were 6.71 and 8.63, respectively). Indeed, there was a statistically significant correlation between final Dysfunctional Attitude Scale score and final Beck score for the 41 drug responders ( $r=0.36$ ,  $df=40$ ,  $p<0.02$ ) and a nonsignificant trend in this direction for the 11 placebo responders ( $r=0.50$ ,  $df=10$ ,  $p<0.10$ ).

To evaluate the possibility that the difference in dys-

**FIGURE 1. Pre- and Posttreatment Mean Scores on the Dysfunctional Attitude Scale of Responding and Nonresponding Depressed Patients Given Drug or Placebo and of Normal Control Subjects<sup>a</sup>**

<sup>a</sup>Significant Group by Time interaction ( $F=41.96$ ,  $df=2, 131$ ,  $p<0.0001$ ). Significantly lower score in responders than in nonresponders both before treatment ( $t=2.76$ ,  $df=110$ ,  $p<0.01$ ) and after treatment ( $t=5.74$ ,  $df=110$ ,  $p<0.0001$ ). Significantly lower score in control subjects than in either responders or nonresponders both before treatment ( $t=3.57$ ,  $df=72$ ,  $p<0.001$ , and  $t=5.65$ ,  $df=80$ ,  $p<0.0001$ , respectively) and after treatment ( $t=2.08$ ,  $df=72$ ,  $p<0.05$ , and  $t=5.91$ ,  $df=80$ ,  $p<0.0001$ ).

functional attitude score between the responders and control subjects was due to residual depression, we subdivided the 52 responders (41 drug-treated and 11 placebo-treated) into those who completely recovered (final Hamilton score  $\leq 5$ ) and those who had some residual pathology (Hamilton score = 6–11). Using a post hoc one-way ANOVA (see table 4), we found significant differences among the complete responders, partial responders, nonresponders, and control subjects ( $F=19.60$ ,  $df=3, 130$ ,  $p<0.0001$ ). Pairwise comparisons showed that the patients whose final Hamilton scores were between 6 and 11 were the ones whose scores differed significantly from those of the control subjects; those who had Hamilton scores of 5 or less did not statistically differ from the control subjects.

One interesting finding was that the degree of cognitive dysfunction was related to response to treatment. The higher the scores on the Dysfunctional Attitude Scale the poorer the responses to drug and placebo treatment, which have been associated with 70% and 40% response rates for acute depression, respectively (23). Surprisingly, although pretreatment score on the Dysfunctional Attitude Scale has been found to be a significant predictor of relapse (24, 25), we are aware of no other study that has reported on the role of the Dysfunctional Attitude Scale in predicting response to a controlled trial of somatic or psychosocial treatment. Parker et al. (26) found that the score on the Dysfunctional Attitude Scale did not predict outcome at 6 or 20 weeks for nonendogenously depressed patients, but none of these patients was taking antidepressants and the psychotherapy was not con-



**TABLE 3. Pre- and Posttreatment Scores on the Dysfunctional Attitude Scale of Patients With Endogenous and Nonendogenous Depression and of Normal Control Subjects**

Group	Score on Dysfunctional Attitude Scale <sup>a</sup>					
	Before Treatment <sup>b</sup>		After Treatment <sup>c</sup>		Change <sup>d</sup>	
	Mean	SD	Mean	SD	Mean	SD
Endogenous depression (N=65)	143.02	31.5	132.12	41.5	-10.89	21.8
Nonendogenous depression (N=47)	163.02	37.2	149.02	39.6	-14.00	12.6
Control subjects (N=22)	99.46	22.7	96.05	22.9	-3.41	7.2

<sup>a</sup>Significant Diagnosis by Time interaction ( $F=3.66$ ,  $df=2$ , 131,  $p<0.03$ ).

<sup>b</sup>Score significantly lower in control subjects than in patients with endogenous depression ( $t=3.96$ ,  $df=85$ ,  $p<0.001$ ) or nonendogenous depression ( $t=7.47$ ,  $df=67$ ,  $p<0.0001$ ) and significantly lower in patients with endogenous than nonendogenous depression ( $t=2.36$ ,  $df=110$ ,  $p<0.02$ ).

<sup>c</sup>Score significantly lower in control subjects than in patients with endogenous depression ( $t=3.43$ ,  $df=85$ ,  $p<0.001$ ) or nonendogenous depression ( $t=6.23$ ,  $df=67$ ,  $p<0.0001$ ) and significantly lower in patients with endogenous than nonendogenous depression ( $t=2.03$ ,  $df=110$ ,  $p<0.05$ ).

<sup>d</sup>Significantly less change in control subjects than in patients with either endogenous depression ( $t=2.29$ ,  $df=85$ ,  $p<0.02$ ) or nonendogenous depression ( $t=3.06$ ,  $df=67$ ,  $p<0.01$ ).

trolled. In addition, Parker et al. found that neuroticism did not predict outcome, which is contrary to the findings of other investigators (27, 28). Block and Robins found that the Dysfunctional Attitude Scale score at initial assessment of depressed patients not in treatment predicted maintenance of depressive diagnosis at 10-week follow-up (unpublished findings). However, there was no control for treatment during this 10-week interval. Our study appears to be the first to show that higher dysfunctional attitude scores are associated with poorer response to somatic treatment.

Since it is felt that for depressed outpatients numerous forms of treatment can be efficacious—e.g., interpersonal therapy (29), cognitive therapy (1, 30)—it would be interesting to know whether the assessment of dysfunctional attitudes can play a role in choice of treatment modality. Use of the Dysfunctional Attitude Scale (and other cognitive measures) might yield a subset of depressed patients for whom these attitudes are a prominent depressive etiology and for whom nonbiological treatments (particularly cognitive therapy), either alone or in combination with antidepressants, would be beneficial. When we separated the patients according to their median initial scores on the Dysfunctional Attitude Scale (median score=148.5), the difference in response rate between drug and placebo groups was greater for the patients with scores below the median than for those with scores above the median. Among the patients with initial scores below the median, 27 (75%) of the 36 drug-treated patients and seven (35%) of the 20 placebo-treated patients re-

**TABLE 4. Posttreatment Scores on the Dysfunctional Attitude Scale of Depressed Patients With Complete Response to Drug or Placebo, Partial Responders, Nonresponders, and Normal Control Subjects**

Group	Posttreatment Score on Dysfunctional Attitude Scale <sup>a</sup>	
	Mean	SD
Responders <sup>b</sup>		
Complete responders (Hamilton score $\leq$ 5) (N=18)	107.17	30.9
Partial responders (Hamilton score=6–11) (N=34)	116.68 <sup>c</sup>	32.8
Nonresponders (N=60)	161.60 <sup>d</sup>	35.0
Control subjects (N=22)	96.05	22.9

<sup>a</sup>Significant difference among groups ( $F=19.60$ ,  $df=3$ , 130,  $p<0.0001$ ).

<sup>b</sup>Includes 41 patients who had received drugs and 11 patients who had received placebo.

<sup>c</sup>Significantly higher than score of control subjects ( $t=2.32$ ,  $df=54$ ,  $p<0.05$ ).

<sup>d</sup>Significantly higher than scores of complete responders ( $t=6.19$ ,  $df=76$ ,  $p<0.0001$ ), partial responders ( $t=6.37$ ,  $df=92$ ,  $p<0.0001$ ), and control subjects ( $t=8.01$ ,  $df=80$ ,  $p<0.0001$ ).

sponded ( $\chi^2=7.07$ ,  $df=1$ ,  $p<0.01$ , with Yates' correction factor). For patients with scores above the median value, the rate of response to drug (14 of 41, 34%) was not statistically different from the rate of response to placebo (four of 15, 27%). This suggests that higher dysfunctional attitude scores require more than just pharmacological treatment alone.

The other finding of note is that individuals who were classified as having definite endogenous depression according to the RDC had a lower initial mean dysfunctional attitude score than the nonendogenous patients, even though the patients with endogenous depression tended to have more severe depressive symptoms as measured with the scales we used. No such difference between endogenous and nonendogenous depression was found by Eaves and Rush (4), Zimmerman and Coryell (31), and Giles and Rush (32). Although *DSM-III* and the RDC define endogenous depression on the basis of a set of discrete clinical symptoms, the difference in Dysfunctional Attitude Scale scores noted here gives credence to the old but still common belief that endogenous depressions are biologically determined and that nonendogenous depressions occur in reaction to life events, perhaps in individuals with certain premorbid personality characteristics (33–35). However, it must be pointed out that the patients with endogenous depression still had higher scores than the normal control subjects and that for both the patients with endogenous and nonendogenous depression the higher the score the poorer the response to drug treatment. Whether the Dysfunctional Attitude Scale is relevant in distinguishing nonendogenous and endogenous depression diagnostically and whether the distinction has any utility in terms of treatment outcome for either group remain to be established (36).

There are two important findings from the present study. First, our results give some support for the cognitive model of depression in that while the depressed patients who responded to treatment still had higher dysfunctional attitude scores than did control subjects, suggesting a possible residual trait effect, the clear statistical difference in scores between the responders and nonresponders and the difference between the control subjects and the responders with some residual pathology suggest that the dysfunctional attitudes are significantly dependent on mood. Second, the higher the initial score on the Dysfunctional Attitude Scale the poorer the response to drug treatment or placebo. This suggests that depressed individuals with high degrees of cognitive distortion may require other forms of treatment to alleviate their depressive symptoms.

## REFERENCES

1. Rush AJ, Beck AT: Adults with affective disorders, in *Behavior Therapy in Psychiatric Settings*. Edited by Hersen M, Bellack AS. Baltimore, Williams & Wilkins, 1978
2. Weissman AN: The Dysfunctional Attitude Scale: a validation study. *Dissertation Abstracts International* 1979; 40(B):1389-1390
3. Beck AT: *Depression: Causes and Treatment*. Philadelphia, University of Pennsylvania Press, 1972
4. Eaves G, Rush AJ: Cognitive patterns in symptomatic and remitted unipolar major depression. *J Abnorm Psychol* 1984; 93:31-40
5. Hamilton EW, Abramson LY: Cognitive patterns and major depressive disorder: a longitudinal study in a hospital setting. *J Abnorm Psychol* 1983; 92:173-184
6. Persons JB, Rao PA: Longitudinal study of cognitions, life events, and depression in psychiatric inpatients. *J Abnorm Psychol* 1985; 94:51-63
7. Silverman JS, Silverman JA, Eardley DA: Do maladaptive attitudes cause depression? *Arch Gen Psychiatry* 1984; 41:28-30
8. Hamilton M: Development of a rating scale for primary depressive illness. *Br J Clin Psychol* 1967; 6:278-296
9. Beck AT, Beamsderfer A: Assessment of depression: the depression inventory, in *Psychological Measurements in Psychopharmacology*. Edited by Pichot P. Basel, Karger, 1974
10. Guy W (ed): *ECDEU Assessment Manual for Psychopharmacology*: Publication ADM 76-338. Rockville, Md, US Department of Health, Education, and Welfare, 1976
11. Raskin A, Schulterbrandt J, Reatig N, et al: Replication of factors of psychopathology in interview, ward behavior, and self-ratings of hospitalized depressives. *J Nerv Ment Dis* 1969; 149: 87-98
12. Endicott J, Spitzer RL: A diagnostic interview: the Schedule for Affective Disorders and Schizophrenia. *Arch Gen Psychiatry* 1978; 35:837-844
13. Spitzer RL, Endicott J, Robins E: Research Diagnostic Criteria: rationality and reliability. *Arch Gen Psychiatry* 1978; 35:773-782
14. Peselow ED, Stanley M, Wolkin A, et al: Clinical features, DST, and response to placebo in depressed outpatients, in *New Directions in Affective Disorders*. Edited by Lerer B, Gershon S. New York, Springer-Verlag, 1989
15. Oliver JM, Baumgart EP: The Dysfunctional Attitude Scale: psychometric properties and relation to depression in an unselected adult population. *Cognitive Therapy and Research* 1985; 9:161-168
16. Stark P, Hardison CD: A review of multicenter controlled studies of fluoxetine vs imipramine and placebo in outpatients with major depressive disorder. *J Clin Psychiatry* 1985; 46(3, section 2):53-58
17. Gelenberg AJ, Wojcik JD, Newell C, et al: A double blind comparison of clovoxamine vs amitriptyline in the treatment of depressed outpatients. *J Clin Psychopharmacol* 1985; 5:30-34
18. Miranda J, Persons JB: Dysfunctional attitudes are mood-state dependent. *J Abnorm Psychol* 1988; 97:76-79
19. Blackburn IM, Jones S, Lewin RJP: Cognitive style in depression. *Br J Clin Psychol* 1987; 24:241-251
20. Hollon SD, Kendall PC, Lumry A: Specificity of depressotypic cognitions in clinical depression. *J Abnorm Psychol* 1986; 95: 52-59
21. Simons A, Garfield S, Murphy G: The process of change in cognitive therapy and pharmacotherapy for depression. *Arch Gen Psychiatry* 1984; 41:45-51
22. Zimmerman M, Coryell W, Coryell C, et al: Dysfunctional attitudes and attributional style in healthy controls and patients with schizophrenia, psychotic depression and non-psychotic depression. *J Abnorm Psychol* 1986; 95:403-405
23. Morris JB, Beck AT: The efficacy of antidepressant drugs: a review of research (1958-1972). *Arch Gen Psychiatry* 1974; 30:667-674
24. Rush AJ, Weissenburger J, Eaves G: Do thinking patterns predict depressive symptoms? *Cognitive Therapy and Research* 1986; 10:225-236
25. Simons AD, Murphy G, Levine JL, et al: Cognitive therapy and pharmacotherapy for depression: sustained improvement over one year. *Arch Gen Psychiatry* 1986; 43:43-48
26. Parker G, Tennant C, Blignault I: Predicting improvement in patients with non-endogenous depression. *Br J Psychiatry* 1985; 146:132-139
27. Frank E, Kupfer DJ, Jacob M, et al: Personality features and response to acute treatment in recurrent depression. *J Personality Disorders* 1987; 1:14-26
28. Hirschfeld RMA, Klerman GL, Andreasen NC, et al: Psychosocial predictors of chronicity in depressed patients. *Br J Psychiatry* 1986; 148:648-654
29. Weissman MM, Klerman GL, Prusoff BA, et al: Depressed outpatients: results one year after treatment with drugs and/or interpersonal psychotherapy. *Arch Gen Psychiatry* 1981; 38:51-55
30. Kovacs M, Rush AJ, Beck AT, et al: Depressed outpatients treated with cognitive therapy or pharmacotherapy. *Arch Gen Psychiatry* 1981; 38:24-29
31. Zimmerman M, Coryell W: Dysfunctional attitudes in endogenous and non-endogenous depressed inpatients. *Cognitive Therapy and Research* 1986; 10:339-346
32. Giles DE, Rush AJ: Relationship of dysfunctional attitudes and dexamethasone in endogenous and non-endogenous depression. *Biol Psychiatry* 1982; 17:1303-1314
33. Gillespie RD: The clinical differentiation of types of depression. *Guy's Hospital Reports* 1929; 9:306-344
34. Kiloh LG, Garside RF: The independence of neurotic depression and nonendogenous depression. *Br J Psychiatry* 1963; 109: 451-463
35. Lewis A: States of depression: their clinical and aetiological classification. *Br Med J* 1938; 2:875-878
36. Robins CJ, Block P, Peselow ED: Endogenous and non-endogenous depressions: relations to life events, personality, and event perceptions. *Br J Clin Psychol* (in press)



# Clonazepam Treatment of Tardive Dyskinesia: A Practical GABAmimetic Strategy

Gunvant K. Thaker, M.D., James A. Nguyen, M.D., Milton E. Strauss, Ph.D.,  
Richard Jacobson, M.D., Bruce A. Kaup, M.D., and Carol A. Tamminga, M.D.

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*Because of the efficacy of specific  $\gamma$ -aminobutyric acid (GABA) agonists in tardive dyskinesia, the authors tested the benzodiazepine clonazepam in a 12-week, double-blind, placebo-controlled, randomized crossover trial in 19 chronically ill patients with tardive dyskinesia who were being treated with neuroleptics. They found a 35% decrease in dyskinesia ratings with clonazepam treatment. The six patients with predominantly dystonic symptoms showed greater benefit than the 13 patients with predominantly choreoathetoid dyskinesias. Tolerance developed to the antidyskinetic effect of clonazepam in the five patients whose long-term use of the drug was followed, but a 2-week clonazepam-free period recaptured its antidyskinetic effect.*

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There are no highly effective drug treatments for tardive dyskinesia (1). Although dopamine-blocking agents are effective in suppressing dyskinetic symptoms (2–4), they can potentially worsen the symptoms or prevent the natural regression of tardive dyskinesia (5, 6). In recent years, attention in tardive dyskinesia therapeutics has focused on  $\gamma$ -aminobutyric acid (GABA) agonist drugs (7–13; unpublished 1982 paper of P. Sevestre et al.). Initially, clinical evaluation of these drugs was based on the hypothesis that striatonigral GABAergic pathways provide a negative “feedback” to the nigral dopaminergic cells, thus reducing their activity (14). Now, however, clinical application is based on studies that implicate GABAergic neurons in the substantia nigra pars reticulata as critical medi-

ators of dyskinetic movements (15). These substantia nigra pars reticulata GABA-containing neurons project to the thalamus, superior colliculus, and reticular formation, forming an important inhibitory efferent pathway from the basal ganglia. Disruption of these GABAergic efferents can produce hyperkinetic involuntary movements in experimental animals (16). On the basis of animal studies, a reduction in nigral GABA-mediated neuronal transmission has been postulated to play a pathophysiological role in tardive dyskinesia (17). Treatments with GABAmimetic drugs demonstrating an antidyskinetic effect would be consistent with this hypothesis.

GABAmimetic treatments vary in their antidyskinetic efficacy in tardive dyskinesia. Early studies with putative GABAergic drugs (e.g., baclofen and valproic acid) (18–21) generally showed little therapeutic promise for these compounds in tardive dyskinesia. Baclofen was only inconsistently found to have an antidyskinetic action. Now, however, it is known to act selectively on a subpopulation of GABA receptors (GABA<sub>B</sub> sites), which may not be relevant to GABA-mediated antidyskinetic action (22). Valproic acid, also inactive in tardive dyskinesia, had only weak, if any, central GABAmimetic effect at the doses used (1400 to 3000 mg/day) in clinical trials reported in 1976 (23). On the other hand, later treatment trials using more specific and potent GABA<sub>A</sub> agonists were encouraging. The first trial using the potent GABA<sub>A</sub> agonist muscimol in tardive dyskinesia (7) reported a mean 45% reduction in dyskinetic symptoms in seven patients. Following that, positive results were also obtained with other direct (e.g., progabide) (unpublished 1982 paper of P. Sevestre et al.) and indirect (e.g.,  $\gamma$ -acetylenic GABA and  $\gamma$ -vinyl GABA) (8–12) GABA agonist drugs. Less encouraging (17) or negative (24) results have been reported with another GABA agonist, 4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3(2H)-one (THIP), which is active only at a subpopulation of GABA<sub>A</sub> receptors (25). Even though several specific GABA<sub>A</sub> agonists have been found to have an effective antidyskinetic action (7–13, 16; unpublished 1982 paper of P. Sevestre et al.), clinical side effects have precluded their further clinical application.

Benzodiazepine receptors, with a subpopulation of GABA<sub>A</sub> receptors, form the GABA-benzodiazepine-

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chloride ion channel complex (26). Benzodiazepines act at this site to facilitate GABA-mediated transmission, thus acting as indirect GABA<sub>A</sub> agonists. Benzodiazepines are widely used clinically as anxiolytics and are less toxic than other GABAmimetics currently available. Based on the efficacy of GABAergic drugs in tardive dyskinesia and the GABAmimetic action of benzodiazepines, we tested the benzodiazepine clonazepam in patients with tardive dyskinesia. The study was done to identify a practical GABAmimetic treatment for this dyskinetic disorder. Clonazepam was evaluated in a double-blind, randomized, placebo-controlled trial in chronically ill patients who were being treated with neuroleptics.

## METHOD

### Subjects

Patients were recruited from the Motor Disorder Clinic at the Maryland Psychiatric Research Center. Patients with tardive dyskinesia who were between 18 and 65 years old and who had no major medical problems were offered the clonazepam treatment protocol. Twenty-two patients gave their voluntary consent to participate in the study after its nature had been explained to them. Three of these patients dropped out of the study for reasons unrelated to the drug effect (one had a psychotic relapse, one withdrew consent to the double-blind procedure, and one lacked transportation). All dropouts occurred early in the protocol, before active clonazepam treatment began. The mean  $\pm$  SD age of the remaining 19 patients was  $39.14 \pm 10.1$  years. Eighteen of the participants had been receiving neuroleptics chronically at a mean chlorpromazine-equivalent dose of  $1291 \pm 1372$  mg/day; one patient was neuroleptic free. All the patients receiving neuroleptics were maintained on the same dose for 4 weeks before initiation of the clonazepam trial and throughout the protocol.

All of the patients met research diagnostic criteria for persistent tardive dyskinesia (27): four patients had mild tardive dyskinesia, nine had moderate symptoms, and six had severe symptoms. Seventeen also had a *DSM-III* diagnosis of chronic schizophrenia, one of schizoaffective disorder, and one of bipolar disorder, manic. Five of the 19 participants were treated for 6–12 months after the initial 12-week study in an open design with clonazepam to evaluate the long-term effect of benzodiazepine administration on tardive dyskinesia. The mean age of these five patients was  $37.2 \pm 7.6$  years. All five patients were receiving concurrent neuroleptic drugs.

### Study Design

The 19 patients were clinically divided into two groups—patients with predominantly dystonic move-

**TABLE 1. Characteristics of Patients With Primarily Dystonic or Choreoathetoid Tardive Dyskinesia Who Were Given Neuroleptics Plus Clonazepam**

Characteristic	Patients With Dystonic Movements (N=6)		Patients With Choreoathetoid Movements (N=13)	
	Mean	SD	Mean	SD
Age (years)	38.23	5.53	40.04	11.82
Chlorpromazine-equivalent neuroleptic dose (mg/day)	1171	1411	1411	1355
Clonazepam dose (mg/day)	3.83	0.68	3.65	0.89
Baseline score on Maryland Psychiatric Research Center Movement Disorder Scale	25.8	9.7	10.3 <sup>a</sup>	4.7

<sup>a</sup> $t=4.77$ ,  $df=17$ ,  $p<0.001$ .

ments and patients with choreoathetoid tardive dyskinesia. The characteristics of these two groups are described in table 1. Clonazepam was evaluated in these patients in a double-blind, placebo-controlled, randomized crossover trial lasting 12 weeks. An initial week of placebo was followed by the first 4-week treatment period (placebo or clonazepam, randomly assigned) of the crossover followed by 2 weeks of placebo and then the second 4-week clonazepam or placebo administration period. At the end of these 11 weeks, placebo was administered for a final week. The drug was formulated as 0.5 mg of clonazepam or as an identical sucrose placebo capsule. The treating physicians were blind to the treatment. They initiated the 4-week treatment period with two capsules a day and increased the dose by two capsules every 3–4 days. The dose increments were carried out to a maximum of nine capsules/day or until the patients developed unwanted side effects. In the presence of any untoward effects, the dose (number of capsules) was reduced to the maximum tolerated dose. The doses of clonazepam in 11 patients were increased to 4–4.5 mg per day of clonazepam; six patients received 3 mg/day, and two patients received 2 mg/day.

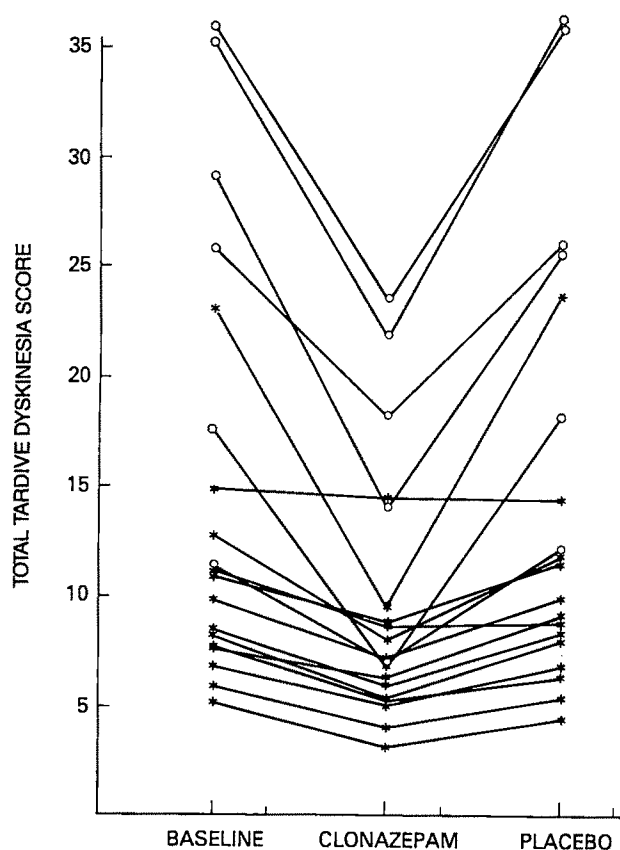
In five patients clonazepam was continued after the double-blind trial in an open long-term treatment design. The maximum tolerated dose reached in the first trial was used for the open follow-up treatment. The patients were followed once every 2–4 weeks; motor evaluations and videotaping were performed for up to 9 months.

### Rating Scale

The Maryland Psychiatric Research Center Movement Disorder Scale, a modification of the Smith Scale (28), was used by the physician weekly in the 12-week study and monthly in the extended administration observation to rate parkinsonian and dyskinetic symptoms. The Brief Psychiatric Rating Scale (BPRS) was



**FIGURE 1.** Effect of Clonazepam or Placebo on Tardive Dyskinesia Scores of Patients With Primarily Dystonic (N=6) or Choreoathetoid (N=13) Movements<sup>a</sup>



<sup>a</sup>Patients with dystonic movements are identified by open circles; patients with choreoathetoid movements are identified by asterisks.

also rated weekly for each patient (29). Videotapes of a standard examination were recorded each week and were rated at a later date by two of us (G.K.T. and J.A.N.) using the Maryland Psychiatric Research Center Movement Disorder Scale. The scores from these videotape ratings were the ones used in the data analysis. The videotape ratings provided a sensitive measure of change in dyskinesia and also helped maintain the study blind for the scorer.

#### Neuropsychological Task

To evaluate possible sedation effect and changes in motor efficiency associated with treatment, patients in the blind study were administered a continuous reaction time test. In this task, the patient touched a lighted square on a cathode ray tube using a light pen. This caused another square to light up, at which time the patient was to lift the pen and touch the other square as rapidly as possible. This procedure assesses both the reaction time (pen lift) and speed of guided movement (time to touch the newly lighted square) concurrently. There were 100 trials in this task, and patients were given a practice session before the initiation of the

clonazepam protocol. They were tested at baseline during the first week of placebo administration and then again at the end of the third week of clonazepam (N=8) or placebo (N=5) administration.

#### Data Analysis

The mean dyskinesia scores obtained from videotaped ratings carried out by two raters were used in the data analysis. The interrater reliability for the videotaped ratings between these two raters was 0.88 (intra-class correlation coefficient) (30). The dyskinesia score during the initial placebo week was taken as a baseline tardive dyskinesia score. The mean of ratings during the second, third, and fourth treatment weeks were counted as the clonazepam or placebo tardive dyskinesia scores. Mean dyskinesia scores during the baseline period and during the clonazepam and placebo periods in the groups of patients with dystonic or choreoathetoid dyskinesias were compared by using a mixed-design analysis of variance (ANOVA) with one between-subject factor, Group, and one within-subject factor, Trials. Post hoc two-tailed *t* tests with Bonferroni's correction were used for individual comparisons. Pooled error terms derived from the ANOVA table, with the sum of squares for both group and interaction error terms, were used for between-group comparisons at each treatment level. The mean square error term for the interaction was used for within-group comparisons (31). Total BPRS scores and BPRS subscale scores were also analyzed by using a mixed design ANOVA with one between-subject and one within-subject factor. Reaction time measures obtained from the five patients given placebo at initial testing and at retesting and the eight patients given placebo at initial testing and clonazepam at retesting were analyzed by using ANOVA. Where appropriate, post hoc two-tailed *t* tests with Bonferroni's correction were used for individual comparisons.

#### RESULTS

Clonazepam treatment reduced dyskinesia scores by 37.1% in the patient group overall, an effect that was reversed during placebo administration (see figure 1). The antidyskinetic effect was more prominent in patients with dystonic (41.5% decrease) than in those with choreoathetoid (26.5% decrease) symptoms. (The percentage decreases in dyskinesia scores were calculated for each individual and then the mean percentages were obtained.) The decrease in scores of the latter group was statistically significant, however. The ANOVA using dyskinesia scores (table 2) indicated significant interaction of the group and repeated measure factors after Huynh-Feldt correction ( $F=17.0$ ,  $df=2, 34$ ,  $p<0.0003$ ). Multiple post hoc comparisons were carried out with the alpha level set at less than 0.005 for statistical significance. In the dystonic group, dyskinesia scores significantly decreased during clon-

**TABLE 2. Tardive Dyskinesia Scores During Clonazepam and Placebo Administration in Patients With Primarily Dystonic or Choreoathetoid Movements<sup>a</sup>**

Condition	Tardive Dyskinesia Score			
	Patients With Dystonic Movements (N=6)		Patients With Choreoathetoid Movements (N=13)	
	Mean	SD	Mean	SD
Baseline	25.8	9.7	10.3	4.7
During clonazepam administration	15.5	7.4	7.1	2.8
During placebo administration	25.7	9.6	9.9	4.9

<sup>a</sup>Results of ANOVA after Huynh-Feldt correction—Group effect:  $F=21.49$ ,  $df=1, 17$ ,  $p<0.0002$ ; Treatment effect:  $F=55.67$ ,  $df=2, 34$ ,  $p<0.0001$ ; Group by Treatment interaction:  $F=16.99$ ,  $df=2, 34$ ,  $p<0.0003$ .

azepam administration compared with baseline ( $t=8.35$ ,  $df=34$ ) and placebo administration ( $t=8.27$ ,  $df=34$ ). The tardive dyskinesia remained unchanged from baseline during placebo administration. In the choreoathetoid group also, the dyskinesia scores were similar during placebo administration and baseline: both were significantly different from baseline and placebo administration during clonazepam treatment ( $t=3.44$  and  $t=3.94$ , respectively,  $df=34$ ). At all study periods (baseline, clonazepam administration, and placebo administration) the dystonic group had significantly higher dyskinesia scores than the choreoathetoid group ( $t=5.21$ ,  $t=2.92$ , and  $t=5.31$ , respectively,  $df=51$ ). Thus, the significant treatment effect of clonazepam was evident in both groups, but there was a greater effect in the dystonic than the choreoathetoid dyskinetic group as indicated by the significant interaction. The post hoc  $t$  test for mean difference between clonazepam administration and baseline scores among dystonic (10.3) and choreoathetoid (3.2) groups was highly significant ( $t=4.20$ ,  $p<0.001$ ).

The total BPRS scores and the BPRS subscale scores of patients during baseline, active drug, and placebo administration periods were unchanged. No significant differences associated with group, treatment period, or their interaction were observed (see table 3).

There was no significant worsening of reaction time during clonazepam administration (see table 4). On the contrary, a slight but nonsignificant improvement in reaction time was noted in patients tested a second time while receiving clonazepam ( $-32$  msec), but reaction time ( $+1$  msec) did not change for those tested both times while receiving placebo. Clonazepam patients, however, had a slower movement time ( $+108$  msec) than the placebo patients ( $+23$  msec) on the second testing (see table 4). The sample size (eight and five patients, respectively) for this between-group comparison was too small for effects of this size to be significant, however.

Six patients experienced mild to moderate sedation;

**TABLE 3. Effect of Clonazepam on BPRS Scores in Patients With Primarily Dystonic or Choreoathetoid Tardive Dyskinesia**

Condition and BPRS Item	Group Score			
	Dystonic (N=6)		Choreoathetoid (N=13)	
	Mean	SD	Mean	SD
Baseline				
Total	26.6	4.0	31.8	10.0
Psychosis	6.5	2.0	10.1	4.9
Anxiety	3.4	1.1	4.1	2.0
Withdrawal	6.3	2.6	7.6	2.6
During clonazepam administration				
Total	26.1	2.4	30.4	9.1
Psychosis	6.7	2.0	9.5	5.2
Anxiety	3.1	1.3	3.1	1.1
Withdrawal	6.2	2.0	7.8	2.0
During placebo administration				
Total	27.9	2.9	32.5	8.7
Psychosis	7.5	1.3	10.4	5.8
Anxiety	3.2	1.1	3.7	1.4
Withdrawal	6.3	2.0	7.8	1.5

**TABLE 4. Effect of Clonazepam on Reaction and Movement Times in Patients With Tardive Dyskinesia**

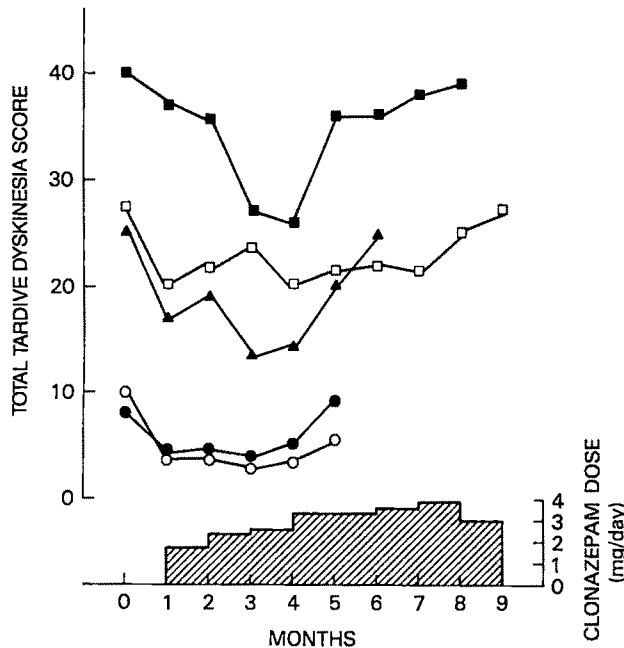
Patient Group and Condition	Reaction Time (msec)		Movement Time (msec)	
	Mean	SD	Mean	SD
Patients given placebo at initial test and retest (N=5)				
Initial test	232	91	164	80
Retest	233	64	187	76
Patients given placebo at initial test and clonazepam at retest (N=8)				
Initial test	252	181	171	104
Retest	220	116	279	159

three complained of ataxia and one of nausea. A drop of 15–20 mm Hg in both diastolic and systolic blood pressure measured at rest in a sitting position was observed in one patient. These side effects were effectively treated with reduction of the dose of clonazepam or placebo. An increase in anxiety in one patient and in dyskinetic symptoms in another were noted during the first week of placebo administration after clonazepam administration. No other side effects were observed clinically. Routine laboratory evaluation of blood and urine samples uncovered no untoward effects with clonazepam treatment.

In five patients, clonazepam was administered for up to 9 months for dyskinetic symptom reduction. These five patients were seen in the clinic every 2–4 weeks to monitor the long-term effect of clonazepam on tardive dyskinesia. The antidyskinetic response just described was observed in all five patients. However, the antidyskinetic actions of the drug disappeared after 5 to 8 months of continuous clonazepam treatment (see figure 2). Clonazepam was gradually withdrawn when



FIGURE 2. Tardive Dyskinesia Scores and Clonazepam Doses During Long-Term Clonazepam Trial in Five Patients With Tardive Dyskinesia<sup>a</sup>



<sup>a</sup>Repeated measures trend analysis showed significant linear ( $F=7.74$ ,  $df=1, 4$ ,  $p<0.05$ ) and quadratic ( $F=24.03$ ,  $df=1, 4$ ,  $p<0.01$ ) components, indicating reversal of the initial antidyskinetic effect.

the tolerance developed to clinically apparent levels. This clonazepam withdrawal was carried out over a period of 1 to 2 weeks. During the gradual clonazepam withdrawal, no significant untoward side effects such as increase in anxiety or insomnia were observed. The patients were kept clonazepam free for 2 weeks and then the benzodiazepine was reinstituted according to the same protocol. The clonazepam again had its robust therapeutic effect on their tardive dyskinesia.

## COMMENT

These data demonstrate an antidyskinetic effect of clonazepam in patients with tardive dyskinesia. Similar results using clonazepam have previously been reported. Bobruff et al. (32) reported marked improvement (over 50%) in tardive dyskinesia in six of 10 patients who received clonazepam at doses ranging from 1 to 10 mg/day. Only one out of 11 patients had as effective an antidyskinetic effect with the comparison drug, phenobarbital. Other investigators (33–46), using either clonazepam or another benzodiazepine (see table 5), have reported antidyskinetic actions. In reviewing these reports, which were mostly case reports or open trials, we learned that 83% of the total 158 patients who received benzodiazepine drugs showed some antidyskinetic response (see table 5). The antidyskinetic effect reported in our study may be less dramatic

than reported previously, but this can be explained by the fact that we used lower doses of the drug to avoid any competing side effects, particularly sedation. The antidyskinetic effect was observed when the clonazepam dose reached 2.0 to 3.5 mg/day. Since high doses were not used, information regarding drug dose and the antidyskinetic response was not obtained.

Interestingly, the antidyskinetic effects were greater in patients with predominantly dystonic movements (41.5% decrease) than in those with clinical choreoathetotic symptoms (26.5% decrease). This cannot be explained by the primary psychiatric diagnosis, mental status changes such as anxiety reduction, or clonazepam dose. It should be noted that patients with dystonic symptoms had a much higher mean tardive dyskinesia score at baseline. One patient with severe choreoathetoid tardive dyskinesia (total score of 23) also showed marked reduction (60.1%) of symptoms with clonazepam. The majority of patients with mild choreoathetoid symptoms did not show such remarkable clinical improvement; however, it is not clear whether a higher clonazepam dose would have further ameliorated their symptoms.

Our findings appear to be independent of sedation, since the gradual dose increments and the optional dose reductions effectively excluded clinical drowsiness in most patients. Furthermore, eight patients were tested for reaction and movement time during baseline and drug treatment to evaluate any mild sedation that could be missed on clinical examination. No increase in reaction time was associated with the clonazepam treatment. On the contrary, there was a nonsignificant decrease in the reaction time, suggesting that the drug dosing strategy was successful in avoiding measurable sedation. Also, reduction in anxiety as an explanation for the antidyskinetic effect is excluded because these patients scored low on the BPRS anxiety subscale and the drug did not show any significant antianxiety effect.

Eventually, tolerance developed to the antidyskinetic effects of the drug. This was not observed in the 12-week protocol, but only in the open study where five patients who were treated chronically developed tolerance within a 3–9 month period (see figure 2). However, by introducing a 2-week clonazepam-free time period, the antidyskinetic efficacy of the drug was easily recaptured.

Clonazepam has a number of neurobiological actions in the mammalian brain. It inhibits the serotonergic neurotransmitter system and has a potent agonist action at the benzodiazepine receptor (47, 48). We propose, however, that the antidyskinetic effect of this drug is due to the indirect GABA agonist actions at the benzodiazepine GABA-chloride channel ionophore. This conclusion is based on the hypothesis that decreased GABA function in the substantia nigra pars reticulata plays a pathophysiological role in tardive dyskinesia (17). Gunne et al. (49) showed that monkeys who develop dyskinetic syndromes with chronic neuroleptic treatment have reductions in GABA synthesis activity in the substantia nigra pars reticulata;

TABLE 5. Studies of Benzodiazepine Treatments in Tardive Dyskinesia<sup>a</sup>

Authors	Year	N	Age (years) <sup>b</sup>	Drug and Daily Dose	Study Design	Comments
Bobruff et al. (32)	1981	21	51.6	Clonazepam, 1–10 mg	Double-blind, phenobarbital controlled	Both drugs had antidyskinetic effect; more dramatic effect observed with clonazepam
Chaturvedi (33)	1987	1	42	Piracetam, 100 mg	Case study, ABA design	—
Cutler (34)	1981	1	52	Clonazepam, 1.5–10 mg	Case report	Tolerance developed after chronic use
Godwin-Austen et al. (35)	1971	6	75–85	Diazepam, 4 mg	Open, placebo-controlled, and tetrabenazine-controlled	Effect of diazepam was same as that of tetrabenazine; both were superior to placebo; sedation with both active drugs
Goswami et al. (36)	1985	1	45	Diazepam, 30 mg	Case report	—
Itil et al. (37)	1974	12	61–86	Clorazepate, 15–45 mg	Open	Slight to marked effect
Kruse (38)	1960	2	50 and 55	Methaminodiazepoxide, 40–75 mg	Case report	“Considerable” improvement
Jacobson et al. (39)	1974	2	18 and 50	Diazepam, 5–20 mg	Case report	Slight improvement in one patient
Mehra et al. (40)	1985	1	— <sup>c</sup>	Alprazolam, 3 mg	Case report	Moderate improvement
O’Flanagan (41)	1975	42	— <sup>c</sup>	Clonazepam, 1–3 mg	Open	Improvement, but sedation was common
Sedman (42)	1976	18	60.8	Clonazepam, 4 mg	Open	11 patients improved (2 markedly, 9 with slight effect); side effects highly prevalent
Singh (43)	1976	3	28.3	Diazepam, 4–30 mg	Case report	Marked improvement without sedation
Singh et al. (44)	1982	21	— <sup>c</sup>	Diazepam, 5–40 mg	Blind	58% decrease in symptoms
Jus et al. (45)	1979	14	45–79	Diazepam, 10 mg i.v.	Open	Marked response
Weber et al. (46)	1983	13	57.4	Diazepam, 5–25 mg	Blind	—

<sup>a</sup>The findings of all of the studies except Weber’s were positive (they found that the benzodiazepine had an antidyskinetic effect); Weber’s findings were negative.

<sup>b</sup>Age, mean age, or age range.

<sup>c</sup>Age not given.

similar changes in the GABA system were not observed in similarly treated monkeys who did not develop dyskinesias. Also, reductions in CSF GABA concentrations specific to tardive dyskinesia have been found in otherwise drug-free schizophrenic patients (17). Pharmacological restoration of the putative hypofunction with a GABA agonist corrects the symptoms (7–13, 50; unpublished 1982 paper of P. Sevestre et al.). In addition, results from our current study further support the therapeutic role of GABAergic drugs in tardive dyskinesia (7–13, 17; unpublished 1982 paper of P. Sevestre et al.). Our study also points to the practical application of benzodiazepines as putative indirect GABA agonists in the treatment of tardive dyskinesia.

The best therapy for an iatrogenic disorder is ultimately its prevention. The advisability of using minimal doses of neuroleptics in clinical practice cannot be overlooked. We also hope that an understanding of the pathogenesis of tardive dyskinesia will lead to the development of superior antipsychotic drugs with lower or no risk of tardive dyskinesia. Use of atypical neuroleptics may allow natural regression of dyskinetic symptoms in patients with tardive dyskinesia, and new

antipsychotic drugs may avoid the risk of causing this motor syndrome altogether. We suggest that drugs like clonazepam be used in the treatment of severe and/or dystonic-type tardive dyskinesias until antipsychotic strategies without a risk of tardive dyskinesia are available.

#### REFERENCES

1. Jeste DV, Wyatt RJ: In search of treatment for tardive dyskinesia: review of the literature. *Schizophr Bull* 1979; 5:251–292
2. Smith RC, Tamminga CA, Haraszti J, et al: Effects of dopaminergic agonists in tardive dyskinesia. *Am J Psychiatry* 1977; 134:763–768
3. Kazamatsuri H, Chien C-p, Cole JO: Long-term treatment of tardive dyskinesia with haloperidol and tetrabenazine. *Am J Psychiatry* 1973; 130:479–483
4. Fog R, Pakkenberg H: Combination treatment of choreiform and dyskinetic syndromes with tetrabenazine and pimozide, in *Tardive Dyskinesia*. Edited by Fann WE, Smith RC, Davis JM, et al. Jamaica, NY, SP Medical & Scientific Books, 1980
5. Glazer WM, Moore DM, Schooler NR, et al: Tardive dyskinesia: a discontinuation study. *Arch Gen Psychiatry* 1984; 41: 623–627
6. Casey DE: Tardive dyskinesia: reversible and irreversible, in *Dyskinesia: Research and Treatment*. Edited by Casey DE,



- Chase TN, Christensen AV, et al. New York, Springer-Verlag, 1985
7. Tamminga CA, Crayton J, Chase T: Improvement in tardive dyskinesia after muscimol therapy. *Arch Gen Psychiatry* 1979; 36:595-598
8. Casey D, Gerlach J, Magelund G, et al: Gamma-acetylenic GABA in tardive dyskinesia. *Arch Gen Psychiatry* 1980; 37: 1376-1379
9. Tell GP, Schechter PJ, Koch-Weser J, et al: Effects of gamma-vinyl GABA. *N Engl J Med* 1981; 305:581-582
10. Tamminga CA, Thaker GK, Hare T, et al: GABA agonist therapy improves tardive dyskinesia. *Lancet* 1983; 2:97-98
11. Korsgaard S, Casey DE, Gerlach J: Effect of gamma-vinyl GABA in tardive dyskinesia. *Psychiatry Res* 1983; 8:261-269
12. Stahl SM, Thornton JE, Simpson ML, et al: Gamma-vinyl GABA treatment of tardive dyskinesia and other movement disorders. *Biol Psychiatry* 1985; 20:888-893
13. Morselli PL, Bossi L, Henry JF, et al: On the therapeutic action of SL 76002, a new GABA-mimetic agent: preliminary observations in neuropsychiatric disorders. *Brain Res Bull* 1980; 5(suppl 2):411-414
14. Gale K, Casu M: Dynamic utilization of GABA in substantia nigra: regulation by dopamine and GABA in the striatum, and its clinical and behavioral implication. *Mol Cell Biochem* 1981; 39:367-405
15. Scheel-Kruger J: Dopamine-GABA interactions: evidence that GABA transmits, modulates, and mediates dopaminergic functions in the basal ganglia and the limbic system. *Acta Neurol Scand Suppl* 1986; 107:1-54
16. Arnt T, Scheel-Kruger J: Intrastriatal GABA antagonists produce dopamine-independent biting in rats. *Eur J Pharmacol* 1980; 62:51-61
17. Thaker GK, Tamminga CA, Alphs LD, et al: Brain gamma-aminobutyric acid abnormality in tardive dyskinesia: reduction in cerebrospinal fluid GABA levels and therapeutic response to GABA agonist treatment. *Arch Gen Psychiatry* 1987; 44:522-529
18. Linnoila M, Viukari M, Hietala O: Effect of sodium valproate on tardive dyskinesia. *Br J Psychiatry* 1976; 129:114-119
19. Chien C, Jung K, Ross-Townsend A: Efficacies of agents related to GABA, dopamine and acetylcholine in the treatment of tardive dyskinesia. *Psychopharmacol Bull* 1978; 14:20-22
20. Gibson AC: Sodium valproate and tardive dyskinesia. *Br J Psychiatry* 1978; 133:82
21. Korsgaard S: Baclofen in the treatment of neuroleptic-induced tardive dyskinesia. *Acta Psychiatr Scand* 1976; 54:17-24
22. Bowery NG, Hill DR, Hudson AL, et al: (-)-Baclofen decreases neurotransmitter release in the mammalian CNS by an action at a novel GABA receptor. *Nature* 1983; 283:92-94
23. Anlezark G, Horton RW, Meldrum BS, et al: Anticonvulsant action of ethanolamine-sulphate and Di-n-propylacetate and the metabolism of gamma-aminobutyric acid (GABA) in mice with audiogenic seizures. *Biochem Pharmacol* 1976; 25:413-417
24. Korsgaard S, Casey DE, Gerlach J, et al: The effect of tetrahydroisoxazopyridinol (THIP) in tardive dyskinesia: a new gamma-aminobutyric acid agonist. *Arch Gen Psychiatry* 1982; 39: 1017-1021
25. Hosli E, Krogsgaard-Larsen P, Hosli L: Autoradiographic localization of binding sites for the gamma-aminobutyric acid analogues 4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridine-3-ol (THIP), isoguvacine and baclofen on cultured neurons of rat cerebellum and spinal cord. *Neurosci Lett* 1985; 61:153-157
26. Haefely W: Benzodiazepine interactions with GABA receptors. *Neurosci Lett* 1984; 47:201-206
27. Schooler NR, Kane JM: Research diagnoses for tardive dyskinesia (letter). *Arch Gen Psychiatry* 1982; 39:486-487
28. Smith RC, Strizich M, Klass D: History of neuroleptic drugs and tardive dyskinesia, in *Tardive Dyskinesia: Research and Treatment*. Edited by Fann WE, Smith RC, Davis JM, et al. Jamaica, NY, SP Medical & Scientific Books, 1980
29. Overall JE, Gorham DR: The Brief Psychiatric Rating Scale. *Psychol Rep* 1962; 10:799-812
30. Bartko JJ, Carpenter WT: On the methods and theory of reliability. *J Nerv Ment Dis* 1976; 163:307-317
31. Winer BJ: *Statistical Principles in Experimental Design*. New York, McGraw-Hill, 1971
32. Bobruff A, Gardos G, Tarsy D, et al: Clonazepam and phenobarbital in tardive dyskinesia. *Am J Psychiatry* 1981; 138: 189-193
33. Chaturvedi SK: Piracetam for drug-induced dyskinesia (letter). *J Clin Psychiatry* 1987; 48:255
34. Cutler NR: Clonazepam and tardive dyskinesia (letter). *Am J Psychiatry* 1981; 138:1127-1128
35. Godwin-Austen RB, Clark T: Persistent phenothiazine dyskinesia treated with tetrabenazine. *Br Med J* 1971; 4:25-26
36. Goswami V, Channabasavanna SM: On the lethality of acute respiratory component of tardive dyskinesia. *Clin Neurol Neurosurg* 1985; 87:99-102
37. Itil TM, Unverdi C, Mehta D: Clorazepate dipotassium in tardive dyskinesia (letter). *Am J Psychiatry* 1974; 131:1291
38. Kruse W: Persistent muscular restlessness after phenothiazine treatment: report of three cases. *Am J Psychiatry* 1960; 117: 152-153
39. Jacobson G, Baldessarini RJ, Manschreck T: Tardive and withdrawal dyskinesia associated with haloperidol. *Am J Psychiatry* 1974; 131:910-913
40. Mehta D, Eaton J, Burch M, et al: Observations in tardive dyskinesia (letter). *J Clin Psychiatry* 1985; 46:73
41. O'Flanagan PM: Clonazepam in the treatment of drug-induced dyskinesia (letter). *Br Med J* 1975; 1:269-270
42. Sedman G: Clonazepam in treatment of tardive oral dyskinesia (letter). *Br Med J* 1976; 2:583
43. Singh MM: Diazepam in the treatment of tardive dyskinesia. *Int J Pharmacopsychiatry* 1976; 11:232-234
44. Singh MM, Becker RE, Pitman RK, et al: Diazepam-induced changes in tardive dyskinesia: suggestions for a new conceptual model. *Biol Psychiatry* 1982; 17:729-742
45. Jus K, Jus A, Gautier J: Studies on the action of certain pharmacological agents on tardive dyskinesia and on the rabbit syndrome. *Int J Clin Pharmacol* 1979; 9:138-145
46. Weber SS, Dufresne RL, Becker RE, et al: Diazepam in tardive dyskinesia. *Drug Intell Clin Pharm* 1983; 17:523-527
47. Pinder RM, Brogden RN, Speight TM, et al: Clonazepam: a review of its pharmacological properties and therapeutic efficacy in epilepsy. *Drugs* 1976; 12:332-361
48. Pratt J, Jenner P, Reynolds EH, et al: Clonazepam induces decreased serotonergic activity in the mouse brain. *Neuropharmacology* 1979; 18:791-799
49. Gunne LM, Haggstrom JE, Sjoquist B: Association with persistent neuroleptic-induced dyskinesia of regional changes in brain GABA synthesis. *Nature* 1984; 309:347-349
50. Dean P, Redgrave P, Eastwood L: Suppression of apomorphine-induced oral stereotypy in rats by microinjection of muscimol into mid-brain. *Life Sci* 1982; 30:2171-2179

# Association Between Family History of Affective Disorder and the Depressive Syndrome of Alzheimer's Disease

Godfrey D. Pearlson, M.D., Christopher A. Ross, M.D., Ph.D.,  
W. David Lohr, M.D., Barry W. Rovner, M.D.,  
Gary A. Chase, Ph.D., and Marshal F. Folstein, M.D.

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*For each of 41 index patients with probable Alzheimer's disease and a first episode of major depression and 71 nondepressed Alzheimer's disease patients, two first-degree relatives were interviewed by a rater blind to presence or absence of depression in the proband. The depressed patients had significantly more first- and second-degree relatives with depression than did control subjects. The lifetime risk for major depression, adjusted for differences in age distribution, was significantly greater in first-degree relatives of index patients, suggesting that depression in Alzheimer's disease is genetically related to primary affective disorder. Alzheimer's disease may be useful for studying aspects of depressive pathophysiology.*

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Depressive symptoms accompanying Alzheimer's disease are not uncommon (1-7) and may be a significant cause of distress and excess disability for Alzheimer's disease patients (8). Whether these symptoms represent major affective disorder is unclear. It is possible that depression is an understandable psychological response to the presence of dementia. However, when present, the depressive syndrome appears to respond to the usual somatic treatments for major depression, suggesting the importance of biologic components in its etiology (9-11).

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Patients with primary depressive illness frequently have family histories of affective disorder (12-14). However, to our knowledge, family history of affective disorder has not been studied in Alzheimer's disease patients with first-episode depression. We therefore conducted a family history study to ascertain whether Alzheimer's disease probands experiencing their first episodes of major depression had more relatives with affective illness than did nondepressed Alzheimer's disease control subjects.

## METHOD

We selected index and comparison subjects from 400 consecutively referred patients who were evaluated at the Johns Hopkins Department of Psychiatry's Dementia Research Clinic between January 1979 and January 1984 for symptoms of cognitive decline beginning in late life. We examined the charts of all such individuals to determine which of them had met criteria for a *DSM-III* diagnosis of primary degenerative dementia and a diagnosis of probable Alzheimer's disease made according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADDA) (15). At the time of assessment each patient was examined by an attending psychiatrist and underwent physical and neurological examinations and relevant blood testing; a detailed history was taken from one or more relatives. Patients with other causes of dementia, CT scans with focal findings, or Hachinski scores (16) higher than 4 were excluded from the study. Each patient's score on the Mini-Mental State Examination (17) was recorded at the time of the initial visit.

We identified 41 patients who were diagnosed by the attending psychiatrist at the time of initial evaluation or at subsequent follow-up as suffering from a major depressive episode. These index patients were independently judged by two of us (G.D.P. and C.A.R.) both to have met the criteria for a major depressive episode according to a *DSM-III* checklist and to have no prior personal history of affective disorder. Negative personal history was initially determined by re-



TABLE 1. Numbers and Ages of First- and Second-Degree Relatives of Depressed and Nondepressed Probands With Alzheimer's Disease

Characteristic	Alzheimer's Disease Plus Depression (N=41)		Uncomplicated Alzheimer's Disease (N=71)		Analysis	
	Mean	SD	Mean	SD	t (df=110)	p
Number of informants interviewed per case	2.0	1.3	1.9	1.1	0.30	n.s.
Number of first-degree relatives						
Total	8.8	4.5	8.0	3.0	1.08	n.s.
Living	4.9	3.8	4.1	2.3	1.30	n.s.
Number of second-degree relatives						
Total	11.1	9.6	5.3	7.0	3.70	0.001
Living	7.6	8.2	3.4	5.0	3.34	0.001
Age of all relatives (years)	52.1	15.5	51.4	15.6	0.21	n.s.

view of relevant records and by questioning one or more informants from the patient's family and the referring physician. In addition, we identified, but excluded from study, 18 individuals with previous clear-cut episodes of affective disorder (all major depression) that predated the onset of the dementia syndrome by many years.

We selected a comparison group of 71 individuals who had been evaluated during the same time period as the index patients, had met the NINCDS/ADRDA criteria for a diagnosis of probable Alzheimer's disease, and were found to be free of any noncognitive psychiatric symptoms (depression, hallucinations, or delusions) at ascertainment and at all subsequent clinic follow-up visits. The index and comparison subjects were followed for a mean of 30 months after initial evaluation.

Of the 41 patients with depression, 29 (71%) were later treated with tricyclic antidepressants; the other patients received a variety of therapies, including ECT and neuroleptics. Subsequently, 23 patients have died (seven were index patients). The diagnosis of Alzheimer's disease was confirmed neuropathologically in 22 cases, and the other patient was found to have abnormalities due to both Alzheimer's disease and multiple infarcts.

A single trained rater, blind to the presence or absence of depression in the proband, attempted to interview at least two family members per proband by telephone. This was accomplished in 85% of the cases. Diagnoses of depression, suicide, and bipolar disorder in first- and second-degree relatives were made according to the Family History Research Diagnostic Criteria (FH-RDC) (18). In these interviews, the absence of previous episodes of affective disorder in the index patients was confirmed. Diagnoses of probable late-life primary degenerative dementia in the relatives were made by using a checklist that combined the FH-RDC with the *DSM-III-R* criteria for primary degenerative dementia.

In the seven cases where family members gave conflicting information, we contacted further relatives, and an attending psychiatrist blind to the presence or absence of depression in the proband was called on to

make the final judgment. Completed suicides and cases of bipolar illness were also tabulated separately.

Significance levels were set at  $p < 0.05$ , continuous variables were analyzed with Student's two-tailed *t* test, and discontinuous variables were analyzed with the chi-square test (with Yates' correction where needed).

## RESULTS

The index (depressed) and comparison probands were not significantly different in age at onset of dementia ( $\text{mean} \pm \text{SD} = 68.5 \pm 8.3$  versus  $69.3 \pm 8.5$  years), age at initial clinic evaluation for Alzheimer's disease ( $72.3 \pm 7.6$  versus  $73.1 \pm 8.1$  years), percentage of female patients (70.7% versus 67.6%), or Mini-Mental State score at initial evaluation ( $16.7 \pm 7.3$  versus  $16.0 \pm 6.8$ ).

For the index group, the time ( $\text{mean} \pm \text{SD}$ ) from the first symptoms of cognitive decline (as noted by their families) to the onset of clinically documented depression was  $17.9 \pm 19.3$  months; depression occurred within 12 months of cognitive decline in 48% of the cases.

The number of informants interviewed per case, numbers of currently living and total first- and second-degree relatives, and age of these relatives are displayed in table 1. There was no significant difference between groups in the number of informants interviewed per case, total number of first-degree relatives, or number of first-degree relatives currently living. Both the total number of second-degree relatives and the number of them currently alive was significantly higher for the index patients. The relatives' mean ages were not significantly different.

As shown in table 2, a positive family history of dementia occurring in late life was present in approximately half of both the index and comparison families, and there were no between-group differences in percentages of affected first-degree, second-degree, or total relatives.

In contrast, a positive family history of major depression was present in significantly more families of

**TABLE 2. Dementia, Depression, and Suicide in First- and Second-Degree Relatives of Depressed and Nondepressed Probands With Alzheimer's Disease**

History and Group	Alzheimer's Disease Plus Depression			Uncomplicated Alzheimer's Disease			Analysis	
	Probands (N=41)		Number of Relatives	Probands (N=71)		Number of Relatives	$\chi^2$ (df=1)	p
	N	%		N	%			
Late-life dementia								
Any relative	19	46.3	49	42	59.2	96	1.21	n.s.
First-degree relatives	18	43.9	33	37	52.1	57	0.70	n.s.
Second-degree relatives	7	17.1	16	20	28.2	39	1.75	n.s.
Depression <sup>a</sup>								
Any relative	23	56.1	30	10	14.1	19	17.91	<0.001
First-degree relatives	19	46.3	22	8	11.3	13	17.61	<0.001
Second-degree relatives	7	17.1	8	3	4.2	6	5.27	<0.05
Completed suicide								
Any relative	9	22.0	11	0	0.0	0	14.11 <sup>b</sup>	<0.001
First-degree relatives	9	22.0	9	0	0.0	0	14.90 <sup>b</sup>	<0.001
Second-degree relatives	3	7.3	3	0	0.0	0	2.99 <sup>b</sup>	n.s.

<sup>a</sup>Cases of suicide contribute to statistics on depression.<sup>b</sup>With Yates' correction.**TABLE 3. Ages at Onset of Dementia and Depression in First- and Second-Degree Relatives of Depressed and Nondepressed Probands With Alzheimer's Disease**

History and Group	Relatives' Age at Onset (years)				Analysis		
	Alzheimer's Disease Plus Depression		Uncomplicated Alzheimer's Disease		t	df	p
	Mean	SD	Mean	SD			
Late-life dementia							
All relatives	73.8	6.6	75.8	7.6	1.00	143	n.s.
First-degree relatives	73.3	7.7	75.8	7.2	1.30	88	n.s.
Second-degree relatives	76.3	6.2	75.2	8.5	1.30	53	n.s.
Depression							
All relatives	43.1	14.6	42.3	14.4	0.15	47	n.s.
First-degree relatives	42.4	13.2	42.5	12.9	0.14	33	n.s.
Second-degree relatives	38.6	16.4	34.6	10.4	0.37	12	n.s.

Alzheimer's disease patients with depression than in the families of the nondepressed probands. Positive family histories of major depression or suicide were found in more than 50% of the index patients. Both the first- and second-degree relatives of the depressed probands had higher rates of depression, excluding suicide, than the relatives of the control probands. Separate analysis of completed suicides revealed a similar and significant association with depression in the proband.

As shown in table 3, there was no significant difference in the age at onset of either dementia or depression between the relatives of the index and comparison groups, either between the total groups or between just the first- or second-degree relatives.

Using a modified life-table method (19), we compared the lifetime risks for major depression in the first-degree relatives of the two groups, estimated by means of the Kaplan-Meier statistic adjusted for differences in age distribution. The lifetime risk was higher in the first-degree relatives of the index patients

than in the first-degree relatives of the comparison patients (17.1% versus 7.7%). This difference was statistically significant ( $\chi^2=4.5$ ,  $df=1$ ,  $p<0.05$ , generalized Savage test).

## DISCUSSION

The major finding of the current study was the association between major depression occurring for the first time in patients with Alzheimer's disease and a high risk of affective disorder in their relatives. Almost half of 41 Alzheimer's disease patients with depression had at least one first-degree relative with major depression, compared with only 11% of nondepressed Alzheimer's disease patients. The lifetime risk for depression in the first-degree relatives of the index patients was over two times as high as in the comparison group, which in turn had a rate comparable to that of the general population (12–14, 20). The contrast between the proportion of probands with affected first-



degree relatives (46%) and their lifetime risk estimate (17%) stems from the counting procedure. If, for example, a proband had six first-degree relatives and only one of them was affected, it would count as a positive finding in determining the number of probands with affected relatives, but in estimating lifetime risk the fraction affected would be taken into account.

This finding was not an artifact due to inclusion of patients with preexisting affective disorder, since such patients (who would be expected to have family histories of depression) were excluded from the study. Other factors that might influence the presence of depression, such as gender, age at onset of dementia, age, or Mini-Mental State score at initial evaluation for dementia, were not different in the index and comparison groups. There was a difference between the groups in total number of second-degree relatives, but we do not believe this affected our finding. The lifetime risk for depression was clearly higher in the first-degree relatives of the index patients, and the number of these relatives did not differ between groups.

The prevalence of major depression in the first- and second-degree relatives of our index patients is similar to expected prevalences in relatives of nondemented probands with major depressive diagnoses (12–14). Despite the exclusion of 18 Alzheimer's disease patients with preexisting major depression, there were still high numbers of both first- and second-degree relatives with major depression in the index group. This enabled us to address specifically the issue of depression first manifesting itself after the onset of Alzheimer's disease. The percentages of relatives with late-life dementia in both the index and comparison groups were consistent with previous estimates (21–23).

Our diagnoses of major depression were made by using a *DSM-III* checklist. More recently, specific scales for assessment of depressed mood in demented patients have been published (24, 25). The use of such scales would have been important had our patients been more severely cognitively impaired. A subsample of index and comparison patients was independently examined in another recent study (8). In that study (in which the diagnosis of depression was based on concurrent examination with a standardized psychiatric rating instrument), the diagnoses were in close agreement: seven of eight index patients were diagnosed as suffering from major depression, and all of 26 comparison patients were judged not to be depressed. The one index patient not diagnosed as depressed had met the criteria for depression according to chart review but was no longer depressed at the time of re-examination.

The relatively high prevalence of major depression detected in our Alzheimer's disease patients (41 of 400 initial referrals, after patients with prior major depression were eliminated) likely reflects a bias toward referral to a psychiatry-based dementia clinic. If the 18 excluded patients are added to the sample of 41, the total prevalence would be approximately 15%, similar to the 17% obtained by Rovner et al. (8), whose pa-

tient sample partially overlapped ours. In two previous studies on major depressive disorder in Alzheimer's disease that used the *DSM-III* criteria (26, 27) the prevalence rates were 19% and 0%, respectively. In general, the rate we report is in agreement with those from previous similar studies, which have been summarized by Wragg and Jeste (7).

Dementia and affective disorder can coexist in two separate circumstances (6, 28–30). First, depression can occur in the context of a dementing illness, such as Alzheimer's disease; Reifler (6) termed this a "type 2" mixed cognitive-affective disturbance, and Feinberg and Goodman (28) described it as a "dementia with secondary depression." Second, reversible cognitive impairment may occur in the context of major affective disorder ("dementia syndrome of depression" or "pseudodementia") (31–38). We feel confident that our depressed patients did not have this latter syndrome, since the onset of their dementia preceded that of their affective symptoms and their Mini-Mental State scores were still abnormal after standard treatment of the depression, which was successful in more than 80% of the cases. Their dementia continued to progress as they were followed within the dementia clinic (their Mini-Mental State scores fell by a mean of 3.7 points per 12 months). Finally, the diagnosis of Alzheimer's disease was pathologically confirmed in a subset of cases.

The neuropathologic basis of secondary depression in Alzheimer's disease is unknown. Cognitive symptoms in Alzheimer's disease are closely associated with deficits in the cholinergic system (39). Cholinergic mechanisms may also play a role in affective disorders (40). As it evolves, Alzheimer's disease also affects noncholinergic neurotransmitter systems in the brainstem, including locus coeruleus noradrenergic and raphe serotonergic systems (41–45). It is possible that monoamine systems are involved in the genesis of noncognitive symptoms (46, 47).

Our results suggest that depression in Alzheimer's disease is related by family history to the depression of primary affective disorder. Alzheimer's disease as it evolves may interact with an existing genetic vulnerability to affective disorder, which is not expressed until the degenerative changes of Alzheimer's disease unfold. This may make Alzheimer's disease a useful model system for studying aspects of depression.

#### REFERENCES

1. Sim M, Sussman I: Alzheimer's disease: its natural history and differential diagnosis. *J Nerv Ment Dis* 1962; 135:489–499
2. Miller NE: The measurement of mood in senile brain disease: examiner ratings and self-reports, in *Psychopathology in the Aged*. Edited by Cole JO, Barrett JE. New York, Raven Press, 1980
3. Reifler BV, Larson E, Hanley R: Coexistence of cognitive impairment and depression in geriatric outpatients. *Am J Psychiatry* 1982; 139:623–626
4. Devanand DP, Nelson JC: Concurrent depression and dementia: implications for diagnosis and treatment. *J Clin Psychiatry* 1985; 46:389–392

5. Reifler BV, Larson E, Teri L, et al: Dementia of the Alzheimer's type and depression. *J Am Geriatr Soc* 1986; 34:855-859
6. Reifler BV: Mixed cognitive-affective disturbances in the elderly: a new classification. *J Clin Psychiatry* 1986; 47:354-356
7. Wragg RE, Jeste DV: Overview of depression and psychosis in Alzheimer's disease. *Am J Psychiatry* 1989; 146:577-587
8. Rovner BW, Broadhead J, Spencer M, et al: Depression and Alzheimer's disease. *Am J Psychiatry* 1989; 146:350-353
9. Snow SS, Wells CE: Case studies in neuropsychiatry: diagnosis and treatment of coexistent dementia and depression. *J Clin Psychiatry* 1981; 42:439-441
10. Reifler BV, Teri L, Raskind M, et al: Double-blind trial of imipramine in Alzheimer's disease patients with and without depression. *Am J Psychiatry* 1989; 146:45-49
11. Liang RA, Lam RW, Ancill RJ: ECT in the treatment of mixed depression and dementia. *Br J Psychiatry* 1988; 152:281-284
12. Baron M, Klotz J, Mendlewicz J, et al: Multiple-threshold transmission of affective disorders. *Arch Gen Psychiatry* 1981; 38:79-84
13. Gershon ES, Hamovitz J, Guroff JJ, et al: A family study of schizo-affective, bipolar I, bipolar II, unipolar, and normal control probands. *Arch Gen Psychiatry* 1982; 39:1157-1167
14. Reich T, Van Eerdewegh P, Rice J, et al: The familial transmission of primary major depressive disorder. *J Psychiatr Res* 1987; 21:613-624
15. McKhann G, Drachman D, Folstein M, et al: Clinical diagnosis of Alzheimer's disease: report of the NINCDS/ADRDA work group. *Neurology* 1984; 34:939-944
16. Hachinski VC, Lassen NA, Marshall J: Multi-infarct dementia. *Lancet* 1974; 1:207-210
17. Folstein MF, Folstein SE, McHugh PR: Mini-Mental State: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12:189-198
18. Andreasen NC, Endicott J, Spitzer RL, et al: The family history method using diagnostic criteria: reliability and validity. *Arch Gen Psychiatry* 1977; 34:1229-1235
19. Chase GA, Folstein MF, Breitner JCS, et al: The use of life tables and survival analysis in testing genetic hypotheses, with an application to Alzheimer's disease. *Am J Epidemiol* 1983; 117:590-597
20. Weissman MW, Myers JK: Affective disorders in a US urban community. *Arch Gen Psychiatry* 1978; 35:1304-1311
21. Breitner JCS, Folstein MF: Familial Alzheimer dementia: a prevalent disorder with specific clinical features. *Psychol Med* 1984; 14:63-80
22. Mohs RC, Breitner JCS, Silverman JM, et al: Alzheimer's disease: morbid risk among first-degree relatives approaches 50% by 90 years of age. *Arch Gen Psychiatry* 1987; 44:405-408
23. Breitner JCS, Silverman JM, Mohs RC, et al: Familial aggregation in Alzheimer's disease. *Neurology* 1988; 38:207-212
24. Sunderland T, Alterman IS, Yount D, et al: A new scale for the assessment of depressed mood in demented patients. *Am J Psychiatry* 1988; 145:955-959
25. Alexopoulos GS, Abrams RC, Young RC, et al: Cornell Scale of Depression in Dementia (CSDD), in *New Research Abstracts, 138th Annual Meeting of the American Psychiatric Association*. Washington, DC, APA, 1985
26. Reding MJ, Haycox J, Blass J: Depression in patients referred to a dementia clinic. *Arch Neurol* 1985; 42:894-896
27. Cummings JL, Miller B, Hill MA, et al: Neuropsychiatric aspects of multi-infarct dementia and dementia of the Alzheimer type. *Arch Neurol* 1987; 44:389-393
28. Feinberg T, Goodman B: Affective illness, dementia and pseudodementia. *J Clin Psychiatry* 1984; 45:99-103
29. Kneisevich JW, Martin RL, Berg L, et al: Preliminary report on affective symptoms in the early stages of senile dementia of the Alzheimer type. *Am J Psychiatry* 1983; 140:233-235
30. Kral VA: The relationship between senile dementia (Alzheimer type) and depression. *Can J Psychiatry* 1983; 28:304-306
31. Morstyn R, Hochanadel G, Kaplan E, et al: Depression vs pseudodepression in dementia. *J Clin Psychiatry* 1982; 43:197-199
32. Wells CE: Pseudodementia. *Am J Psychiatry* 1979; 136:895-900
33. Shraberg D: The myth of pseudodementia: depression and the aging brain. *Am J Psychiatry* 1978; 135:601-603
34. McAllister TW, Price TRP: Severe depressive pseudodementia with and without dementia. *Am J Psychiatry* 1982; 139:626-629
35. McAllister TW: Overview: pseudodementia. *Am J Psychiatry* 1983; 140:528-533
36. Nott PN, Fleminger JJ: Presenile dementia: the difficulties of early diagnosis. *Acta Psychiatr Scand* 1975; 51:210-217
37. Liston EH: Diagnostic delay in presenile dementia. *J Clin Psychiatry* 1978; 39:599-603
38. Lazarus LW, Newton N, Cohler B, et al: Frequency and presentation of depressive symptoms in patients with primary degenerative dementia. *Am J Psychiatry* 1987; 144:41-45
39. Coyle JR, Price DL, DeLong MR, et al: Alzheimer's disease: a disorder of cortical cholinergic innervation. *Science* 1983; 219:1184-1190
40. Janowsky DS, Risch SC: Role of acetylcholine mechanisms in the affective disorders, in *Psychopharmacology: The Third Generation of Progress*. Edited by Meltzer HY. New York, Raven Press, 1987
41. Tomlinson BE, Irving D, Blessed G: Cell loss in the locus coeruleus in senile dementia of the Alzheimer type. *J Neurol Sci* 1981; 49:419-428
42. Palmer AM, Wilcock GK, Esiri M, et al: Monoaminergic innervation of the frontal and temporal lobes in Alzheimer's disease. *Brain Res* 1987; 401:231-238
43. Mann DMA, Yates PO: Serotonin nerve cells in Alzheimer's disease (letter). *J Neurol Neurosurg Psychiatry* 1983; 46:96
44. Bondareff W, Mountjoy CQ, Roth M: Selective loss of neurones of origin of adrenergic projection to cerebral cortex (nucleus locus coeruleus) in senile dementia (letter). *Lancet* 1981; 1:783-784
45. Cross A, Crow J, Ferrier I, et al: Serotonin receptor changes in dementia of the Alzheimer type. *J Neurochem* 1984; 43:1574-1581
46. Zweig RM, Ross CA, Hedreen JC, et al: The neuropathology of aminergic nuclei in Alzheimer's disease. *Ann Neurol* 1988; 24:233-242
47. Zubenko GS, Moosy J: Major depression in primary dementia: clinical and neuropathologic correlates. *Arch Neurol* 1988; 45:1182-1186



# Relapse Following Discontinuation of Lithium Maintenance Therapy in Adolescents With Bipolar I Illness: A Naturalistic Study

Michael Strober, Ph.D., Wendy Morrell, M.S.W.,  
Carlyn Lampert, M.S.W., and Jane Burroughs, M.S.W.

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*The authors conducted an 18-month naturalistic prospective follow-up study of 37 adolescents whose bipolar I illness had been stabilized with lithium carbonate during inpatient hospitalization. Thirteen of the patients discontinued prophylactic lithium therapy shortly after discharge. The relapse rate of bipolar illness in these 13 patients was nearly three times higher than the rate in patients who continued lithium prophylaxis without interruption. Early relapse among lithium-treated patients was associated with a greater risk of relapsing again. The authors discuss the theoretical and clinical implications of these findings.*

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Although bipolar illness is often thought of as an adult condition, some 15% to 30% of those affected experience their first manic or depressive episode before age 20 (1, 2). Adolescent bipolar patients are generally assumed to require preventive lithium therapy following remission of acute symptoms, but controlled studies are lacking and descriptive accounts of the course of prophylactic lithium treatment in this age group are sparse (3).

In the present study a naturalistic design was used to examine the frequency of manic and depressive relapses in a well-characterized sample of adolescent patients with bipolar I illness during the 18 months following their stabilization with lithium carbonate. Failure rates of patients who were noncompliant with recommended maintenance therapy and patients who continued to take the drug were compared throughout

the follow-up period to assess the potential efficacy of lithium prophylaxis in this age group.

## METHOD

### Subjects

The sample consisted of 16 girls and 21 boys, 13 to 17 years of age (mean age=15.1 years), who met strictly applied DSM-III criteria for a manic episode and Research Diagnostic Criteria (RDC) (4) for bipolar disorder with mania (bipolar I disorder) and who had no concurrent or preceding mood-incongruent psychotic features. All patients were selected from consecutive admissions to the adolescent service of the University of California, Los Angeles, Neuropsychiatric Institute. Diagnoses represent the consensus judgment of two highly experienced clinicians and were based on structured interviews using the Schedule for Affective Disorders and Schizophrenia (5), observation of hospital course, and information obtained from parents on the onset and chronology of the patient's disturbance. In addition, the family psychiatric history was obtained from parents by using the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (6) and the Family History Research Diagnostic Criteria (7) and blindly diagnosed by using a best-estimate procedure described elsewhere (8). To be included in the study patients also had to meet the following additional criteria: no more than 3 months of sustained treatment with lithium, carbamazepine, or other antimanic agents before the index hospitalization; a Raskin Severity of Mania Scale (9) score of 7 or more; a nursing global rating of manic severity on the 15-point Bunney-Hamburg Scale (10) of 8 or more (moderate); good physical health, normal clinical laboratory values, and no history of neurological deficit or abnormality; and WISC-R IQ of 80 or more. Of the 37 patients, 16 had had episodes of depression or mania fitting RDC before the index hospitalization. No patient met conventional criteria for rapid cycling (four or more episodes per calendar year).

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Received Aug. 5, 1988; revision received Oct. 3, 1989; accepted Oct. 31, 1989. From the Child and Adolescent Mood Disorders Program, Neuropsychiatric Institute and Hospital, University of California School of Medicine, Los Angeles. Address reprint requests to Dr. Strober, Child and Adolescent Mood Disorders Program, UCLA Neuropsychiatric Institute, 760 Westwood Plaza, Los Angeles, CA 90024.

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### *Acute Phase*

Treatment with lithium carbonate began during the first week of hospitalization following completion of the patient's initial diagnostic workup. Dose increases were titrated according to side effects and clinical response to achieve plasma levels in the recommended therapeutic range. Neuroleptic drugs were used adjunctively for agitation or psychosis in 16 patients, and lithium was augmented with carbamazepine during the acute phase in four patients. Adjustments of lithium serum levels immediately following stabilization of the index episode yielded values ranging from 0.7 to 1.4 mEq/liter. During the acute phase all patients were assessed weekly with the Manic State Rating Scale (11), the Hamilton Rating Scale for Depression (12), and the Clinical Global Impression scale (CGI) (13). Patients were considered stable if they met the following a priori criteria for a minimum of 4 weeks: Raskin Severity of Mania Scale score of 5 or less, Hamilton depression scale score of 7 or less, a 50% or greater reduction in Manic State Rating Scale and Bunney-Hamburg Scale scores, and a minimum CGI rating of much improved.

### *Follow-Up Procedures*

All patients were treated in the hospital until they met criteria for stabilization. Thereafter, they received outpatient care, with the recommendation that maintenance lithium therapy be continued without interruption through adolescence. Despite the lack of current guidelines regarding maintenance therapy in juveniles, this is standard practice at our center even for patients who have had their first episode of illness. We base this policy on current knowledge of recurrence risks in bipolar illness and the potentially debilitating effects of recurrences during the adolescent years. Before the patient's discharge, each family received extensive education concerning the nature of bipolar illness and the role of lithium and other pharmacological agents in its management. The treating physicians, all of whom were known to us, were aware that their patients' status would be monitored prospectively over the course of 18 months and pledged cooperation with the study. Lithium serum levels were monitored every 4 to 6 weeks, and additional checks were conducted if there was evidence of exacerbation of symptoms or when noncompliance was suspected. All patients received adjunctive individual and family therapy, although the frequency, duration, and intensity of these therapies varied widely. Decisions regarding the type and frequency of psychosocial interventions were made entirely by the treating outpatient physician.

Patients were assessed at each visit by their physician using the Hamilton depression scale, the Manic State Rating Scale, and a manic-depression diagnostic symptom checklist, supplemented with information on the patient's clinical status and medication compliance supplied by parents and other informants. These

assessments were reviewed with a member of the research team once a month. In addition, patients were seen by research staff within several days of onset of symptom exacerbations. For this study, relapse was defined as symptom exacerbations meeting RDC for major depressive disorder or manic disorder; in all but one instance relapse resulted in the patient's rehospitalization.

Twenty-four (64.9%) of the 37 patients continued their maintenance lithium therapy without interruption throughout the 18-month follow-up period; they are referred to here as completers. Eighteen completers received lithium alone; three received low doses of a neuroleptic drug in combination with lithium during the entire 18 months; two received supplemental neuroleptic drugs only during the first 6 months of follow-up; and one patient received carbamazepine in combination with lithium for the duration of follow-up. The mean  $\pm$  SD lithium serum level in these 24 patients during the 18 months was 0.79 mEq/liter (range=0.6–1.2 mEq/liter).

Thirteen (35.1%) of the patients discontinued their lithium against medical advice at some point during follow-up while they were still asymptomatic; they are referred to here as noncompleters. At the time of discontinuation these 13 patients had been taking lithium for a mean of 3.92 months (range=less than 1 month to 12 months); 11 of the 13 received less than 6 months of maintenance therapy before discontinuation, and eight of the 13 discontinued their lithium less than 3 months after discharge. A patient was considered to have discontinued medication if his or her serum lithium level dropped below 0.6 mEq/liter for more than 3 consecutive months. Patients who discontinued their medication on subsyndromal exacerbation of symptoms and who subsequently developed full RDC for mania or depression were considered to have failed on lithium (i.e., as completers).

Completers and noncompleters did not differ significantly on any baseline clinical measure and were comparable in regard to age, sex ratio, duration of index episode, time to stabilization, number of previous episodes, proportion with positive family history of bipolar illness, IQ, marital status of parents, and social class. Only the first relapse was considered in the statistical analysis comparing outcome differences between the two groups.

### RESULTS

Twenty-one (56.8%) of the 37 patients relapsed at some point during follow-up. However, the relapse rate among noncompleters was nearly three times higher than for completers: 12 (92.3%) of the 13 noncompleters relapsed, compared with nine (37.5%) of the 24 completers, a highly significant difference ( $p=0.001$ , Fisher exact test). Table 1 summarizes a life table analysis (14) of the cumulative probabilities of relapse at 3-month intervals for each group. It can be



**TABLE 1. Cumulative Probabilities of Relapse Over Time Among Adolescents Who Did or Who Did Not Continue Maintenance Lithium Therapy for 18 Months After Stabilization of Bipolar I Illness**

Time Interval (months)	Probability of Relapse <sup>a</sup>	
	Completers (N=24)	Noncompleters (N=13)
0-3	0.04	0.15
4-6	0.13	0.62
7-9	0.22	0.62
10-12	0.34	0.85
13-15	0.38	0.92
16-18	0.38	0.92

<sup>a</sup>Completers significantly different from noncompleters (Mantel-Cox  $\chi^2=10.96$ ,  $df=1$ ,  $p<0.001$ ).

seen that relapses in each group clustered in the first 12 months of follow-up; however, differences between the two groups were strikingly clear by 6 months, and an overall comparison of the two survival distributions was highly significant (table 1).

The 14 completers who were asymptomatic before the index episode were just as likely to relapse during follow-up as were the 10 completers who had had previous episodes: five (36%) versus four (40%) patients in each group, respectively, had relapses. However, relapses in both groups of completers were less common than they were in the six noncompleters who had and the seven noncompleters who had not had previous episodes ( $p<0.05$  for each pairwise comparison, Fisher exact test). Moreover, as a group, the 10 completers who had had previous episodes had a statistically significant decline in the mean $\pm$ SD number of episodes during follow-up: before lithium they had  $1.70\pm0.78$  episodes and during lithium maintenance they had  $0.8\pm1.00$  episodes (paired  $t=3.21$ ,  $df=9$ ,  $p<0.02$ ).

As a group, the 24 completers experienced a total of 14 relapses during the 18-month follow-up. Seven (50%) of the relapses were manic, four (29%) were depressive, and three (21%) were mixed. Six (25%) of the completers had manic relapses, three (12.5%) had depressive relapses, and three (12.5%) had mixed-state relapses. On the basis of simple univariate comparisons, the patients who did or did not relapse were not found to differ in age, sex, number of episodes before index hospitalization, or family history of bipolar illness. Among the completers alone, no significant differences were found between those who relapsed and those who remained well in regard to age, sex, number of previous episodes, mean lithium serum levels during follow-up, or proportion receiving medications other than lithium.

## DISCUSSION

To our knowledge, this is the first study to assess prospectively the early course of maintenance lithium therapy in adolescents with bipolar illness using strictly defined diagnostic criteria and generally ac-

cepted measures of symptom morbidity and treatment response. In spite of the considerable care paid to educating the families of these children regarding the management of bipolar illness and the known efficacy of lithium in preventing future recurrences, noncompliance with prophylactic treatment still occurred in nearly one-third of the sample, a rate similar to those reported in adult bipolar patients (15). The outcome for the adolescents who did not continue to take lithium was decidedly unfavorable: 92% had a relapsing course of illness, compared with 38% of the adolescents who continued to take the drug. Lithium also appeared to benefit completers who had had episodes before the index hospitalization by reducing their affective morbidity during the follow-up period, a finding of practical importance when set against data that suggest a positive correlation between frequency of previous episodes and greater risk of relapse among patients not treated with prophylactic lithium (16).

The relapse rates among the completers and non-completers in this sample are broadly similar to those reported for drug- and placebo-treated patients in adult studies of lithium prophylaxis—roughly 35% and 85%, respectively (17, 18). Likewise, our findings are in line with numerous other reports in the adult literature of frequent and in many cases rapid reoccurrence of illness on discontinuation of lithium therapy (19–24), although the degree of benefit derived from long-term maintenance lithium under ordinary clinical conditions has been questioned (25).

As in previous investigations of lithium prophylaxis (17, 18), relapses in this sample clustered in the first year of follow-up. Although the small size of the sample precluded use of more powerful multivariate analysis of predictor variables, two trends emerged that bear mention. First, in three studies of adult bipolar patients (26–28), response to lithium in the initial 6 to 12 months of maintenance therapy proved to be a significant predictor of longer-term outcome. This appears to have been the case in our sample as well. Specifically, of the five completers who relapsed in the first 9 months of follow-up, four (80%) had one or more subsequent relapses between 10 and 18 months; in contrast, of the 19 completers who remained well during the first 9 months of follow-up, only four (21%) relapsed thereafter, a statistically significant difference ( $p=0.027$ , Fisher exact test). We did not find, as others (26) have, that treatment failure was more likely in patients who had had affective episodes before initiation of lithium prophylaxis; however, detection of such an association may require study of a larger sample with greater variability in duration of illness. Second, at least five studies (26, 27, 29–31) have demonstrated an association between family history of bipolar illness and more favorable response to lithium prophylaxis, although two studies (28, 32) found no such link. In the present sample, four (29%) of the 14 completers who had family histories of bipolar illness had relapses, compared with five (50%) of the 10 completers without positive family histories. The difference

is nonsignificant, but the trend is worthy of further study in larger samples.

Several limitations of the study deserve comment. Given that the sample size was relatively small, and even though completers and noncompleters did not differ on baseline clinical measures, the possibility that noncompleters as a group were biased toward greater chronicity or lithium refractoriness cannot be discounted. Still, not all variables that might conceivably influence relapse or survival were defined or controlled for. For example, we did not undertake any formal assessment of personality disturbance in these patients, nor did we measure in any objective fashion qualities of the intrafamilial environment (e.g., hostile or critical attitudes toward the patient), both of which have been shown to predict a less favorable response to lithium prophylaxis in adult bipolar patients (27, 33). Indeed, it was our clinical impression that there were generally higher levels of ambient stress and interpersonal discord in the families of noncompleters, but whether noncompleters were any more likely than completers to be targets of excessive criticism or hostile remarks is less clear. Moreover, such discord was not uniformly present in families of noncompleters, whereas relationships in some completer families were highly tempestuous. As to the question of personality disturbances, noncompleters did not differ from completers in the proportion receiving *DSM-III* axis II diagnoses; however, neither psychometric nor interview-based assessments of personality were available.

Second, we acknowledge that the 4-week criterion for stabilization during the acute treatment phase may have been too brief to rule out the possibility that at least some relapses early in the follow-up were exacerbations of partially treated index episodes rather than new episodes of illness.

Third, although every effort was made to monitor compliance and to date the time of lithium withdrawal in noncompleters, these determinations cannot always be made with complete certainty or precision in a naturalistic study. It is possible, therefore, that some relapses in the sample were actually the cause rather than the consequence of lithium discontinuation, since it is not uncommon for patients to halt their medication abruptly when they experience a recurrence of prodromal symptoms that ultimately progress in intensity to full-blown episodes. Such pitfalls underline the obvious importance of attempting replication of the present findings under rigorously controlled double-blind conditions.

A final question concerns the generalizability of these findings across the broader clinical spectrum of bipolar states in adolescents. Of particular theoretical importance in this regard is the contention that bipolar illness in adolescence may be associated with a relatively high incidence of psychoticism, comorbidity, and superimposed neuropsychiatric complications, factors that lead simultaneously to more variable and, possibly, atypical expression of symptoms and greater resistance to lithium treatment (34, 35). In line with

this speculation, Himmelhoch and Garfinkel (34) have remarked on the unusually high proportion of adolescents among the lithium-resistant bipolar patients they have studied. The majority of these young patients presented with mixed states and concomitant neuropsychiatric abnormalities of some sort. Three studies lend further support to the idea that juvenile onset of bipolar illness may, in some patients, represent a particularly virulent genetic and clinical subtype. One, a recent report from our group on a large cohort of adolescent manic patients (8), found significant associations between density of familial aggregation of bipolar illness, prepubertal history of aggressive hyperactivity, and refractoriness to acute lithium therapy. The other two (36, 37) have linked earlier age at onset in bipolar patients to greater familial loading. If juvenile onset delimits a unique genetic and clinical subtype of bipolar illness, the differential efficacy (38) of alternative antimanic compounds in adolescent bipolar patients who fail to respond adequately to preventive lithium therapy remains an issue of obvious critical importance for future therapeutic trials.

#### REFERENCES

1. Kraepelin E: Manic-Depressive Insanity and Paranoia. Translated by Barclay RM; edited by Robertson GM. Edinburgh, E & S Livingstone, 1921
2. Goodwin FK, Jamison KR: The natural course of manic-depressive illness, in *The Neurobiology of Mood Disorders*. Edited by Post RM, Ballenger JC. Baltimore, Williams & Wilkins, 1984
3. Strober M, Hanna G, McCracken J: Bipolar illness, in *Handbook of Child Psychiatric Diagnosis*. Edited by Last C, Hersen M. New York, John Wiley & Sons, 1989
4. Spitzer RL, Endicott J, Robins E: Research Diagnostic Criteria: rationale and reliability. *Arch Gen Psychiatry* 1978; 35:773-782
5. Endicott J, Spitzer RL: A diagnostic interview: the Schedule for Affective Disorders and Schizophrenia. *Arch Gen Psychiatry* 1978; 35:837-844
6. Spitzer RL, Endicott J: Schedule for Affective Disorders and Schizophrenia—Lifetime Version, 3rd ed. New York, New York State Psychiatric Institute, Biometrics Research, 1979
7. Andreasen NC, Endicott J, Spitzer RL, et al: The family history method using diagnostic criteria. *Arch Gen Psychiatry* 1977; 34:1229-1235
8. Strober M, Morrell W, Burroughs J, et al: A family study of bipolar I disorder in adolescence: early onset of symptoms linked to increased familial loading and lithium resistance. *J Affective Disord* 1988; 15:255-268
9. Raskin A, Schulerbrandt J, Reatig N, et al: Replication of factors of psychopathology in interview, ward behavior, and self-ratings of hospitalized depressives. *J Nerv Ment Dis* 1969; 149: 87-98
10. Bunney WE, Hamburg DA: Methods for reliable longitudinal observation of behavior. *Arch Gen Psychiatry* 1963; 9:114-120
11. Blackburn IM, Loudon JB, Ashworth CM: A new scale for measuring mania. *Psychol Med* 1977; 7:453-458
12. Hamilton D: Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol* 1967; 6:278-296
13. Guy W (ed): *ECDEU Assessment Manual for Psychopharmacology*: Publication ADM 76-338. Washington, DC, US Department of Health, Education, and Welfare, 1976
14. Fleiss JL, Dunner DL, Stallone F, et al: The life table: a method for analyzing longitudinal studies. *Arch Gen Psychiatry* 1976; 33:107-112

15. Shaw E: Lithium noncompliance. *Psychiatr Annals* 1986; 16: 583-587
16. Grof P, Angst J, Karasek M, et al: Selection of an individual patient for long-term lithium treatment in clinical practice, in *Lithium: Controversies and Unresolved Issues*. Edited by Cooper TB, Gershon S, Kline NS, et al. Amsterdam, Excerpta Medica, 1979
17. Prien RF: Long-term prophylactic pharmacologic treatment of bipolar illness, in *Psychiatry Update: The American Psychiatric Association Annual Review*, vol 2. Edited by Grinspoon L. Washington, DC, American Psychiatric Press, 1983
18. Cole JO, Chiarello RJ, Merzel APC: Psychopharmacology update: long-term pharmacotherapy of affective disorders. *McLean Hosp J* 1986; 11:106-138
19. Grof P, Cakuls P, Dostal T: Lithium drop outs: a follow-up study of patients who discontinued prophylactic treatment. *Acta Psychiatr Scand* 1970; 5:162-169
20. Bastrup PC, Poulson JC, Schou M, et al: Prophylactic lithium: double-blind discontinuation in manic-depressive disorders. *Lancet* 1970; 2:326-330
21. Cordess C: "Rebound" mania after lithium withdrawal? (letter). *Br J Psychiatry* 1982; 141:431
22. Mander AJ: Is lithium justified after one manic episode? *Acta Psychiatr Scand* 1986; 73:60-67
23. Small JB, Small IF, Moore DF: Experimental withdrawal of lithium in recovered manic-depressive patients: a report of five cases. *Am J Psychiatry* 1971; 127:1555-1559
24. Sashidharan SP, McGuire RJ: Recurrence of affective illness after withdrawal of long-term lithium treatment. *Acta Psychiatr Scand* 1983; 68:126-133
25. Dickson WE, Kendall RE: Does maintenance lithium therapy prevent recurrences of mania under ordinary clinical conditions? *Psychol Med* 1986; 16:521-530
26. Prien RF, Caffey FM, Klett CJ: Factors associated with treatment success in lithium carbonate prophylaxis. *Arch Gen Psychiatry* 1974; 31:189-192
27. Abou-Saleh MT, Coppen A: Who responds to prophylactic lithium? *J Affective Disord* 1986; 10:115-125
28. Dunner DL, Fleiss JL, Fieve RR: Lithium carbonate prophylaxis failure. *Br J Psychiatry* 1976; 129:40-44
29. Mendlewicz J, Fieve RR, Stallone F: Relationship between the effectiveness of lithium therapy and family history. *Am J Psychiatry* 1973; 130:1011-1013
30. Stallone F, Shelley F, Mendlewicz J, et al: The use of lithium in affective disorders, III: a double-blind study of prophylaxis in bipolar illness. *Am J Psychiatry* 1973; 130:1006-1010
31. Maj M, Del Vecchio M, Starace F, et al: Prediction of affective psychoses response to lithium prophylaxis: the role of socio-demographic, clinical, psychological and biological variables. *Acta Psychiatr Scand* 1984; 69:37-44
32. Misra PC, Burns BH: Lithium non-responders in a lithium clinic. *Acta Psychiatr Scand* 1977; 55:32-40
33. Miklewicz DJ, Goldstein MJ, Nuechterlein KH, et al: Family factors and the course of bipolar affective disorder. *Arch Gen Psychiatry* 1988; 45:225-231
34. Himmelhoch JM, Garfinkel ME: Sources of lithium resistance in mixed mania. *Psychopharmacol Bull* 1986; 22:613-620
35. Ballenger JC, Reus VI, Post RM: The "atypical" clinical picture of adolescent mania. *Am J Psychiatry* 1982; 139:602-606
36. Gershon ES: Genetics, in *Manic-Depressive Illness*. Edited by Goodwin FK, Jamison KR. Oxford, Oxford University Press (in press)
37. Rice J, Reich T, Andreasen NC, et al: The familial transmission of bipolar illness. *Arch Gen Psychiatry* 1987; 44:441-450
38. Prien RF, Gelenberg AJ: Alternatives to lithium for preventive treatment of bipolar disorder. *Am J Psychiatry* 1989; 146:840-848



# Plasma Concentrations of Melatonin in Panic Disorder

Iain M. McIntyre, Ph.D., Fiona K. Judd, M.D., Graham D. Burrows, M.D.,  
Stuart M. Armstrong, Ph.D., and Trevor R. Norman, Ph.D.

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*Nocturnal plasma melatonin concentrations were measured in seven patients with panic disorder and eight healthy control subjects. The five patients who had never received psychotropic medication had significantly greater melatonin concentrations from 4:00 a.m. to 7:00 a.m. than the control subjects. In addition it is possible that a phase delay occurred in these unmedicated patients. The findings are discussed in terms of previous studies showing increased melatonin in manic patients and the effect of intense stress on melatonin synthesis. The two patients who had been medication free for only 1 week showed a decreased melatonin rhythm, which is consistent with previous findings in medicated patients.*

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In healthy individuals the pineal gland hormone melatonin exhibits a clearly described circadian rhythm, with low plasma concentrations during daylight hours and peak levels at about 2:00 a.m. (1, 2). In patients with affective disorders, there have been indications of circadian as well as seasonal variation in illness, which may be reflected in melatonin production (3). There are also reports that the amplitude of the nocturnal melatonin peak may be impaired in some disorders. Early investigations that described significantly lowered nighttime melatonin levels in depressed patients (4-6) have been supported by more recent studies (7-9). Furthermore, Lewy et al. (10) reported higher plasma melatonin concentrations in patients with bipolar affective disorder during the manic phase than during the depressed phase. The melatonin concentrations in the manic phase were also higher than those measured in normal control subjects.

Similarities between the biochemical findings in pa-

tients with depressive illness and in patients who experience panic attacks (11) first prompted our investigations into the nocturnal concentrations of melatonin in patients with panic disorder (12, 13). In these two preliminary studies, we found melatonin plasma concentrations to be significantly lower in panic patients than in healthy control subjects. It appeared that, similar to patients with depression, these patients with panic disorder had lower nocturnal melatonin production. However, in both investigations we evaluated melatonin levels up to midnight, and early-morning samples were not collected. As a consequence, the major period of nocturnal melatonin production was not studied. Also, most of the patients were receiving antidepressant and benzodiazepine medications. We have subsequently found that benzodiazepines suppress human nocturnal melatonin (14). Thus, the present investigation was undertaken to further examine the circadian profile of melatonin in a drug-free sample of patients with panic disorder.

## METHOD

Seven patients (five male, two female; mean  $\pm$  SD age =  $31.3 \pm 11.4$  years), who met the *DSM-III-R* criteria for panic disorder with or without phobic avoidance, and eight healthy control subjects (four male, four female; age =  $25.1 \pm 2.0$  years), who had no history of psychiatric disorders, were studied. All of the patients were participating in an outpatient treatment program. Persons with cardiac, renal, hepatic, pulmonary, collagen, or endocrine disease were excluded from the study, as were those with psychiatric diagnoses other than panic disorder. All of the patients were drug free at the time of investigation. Five had never received psychotropic medication, and two had undergone withdrawal from alprazolam and had been drug free for 7 days before the study. All experienced moderate to severe anxiety (mean  $\pm$  SD score on the Hamilton Rating Scale for Anxiety was  $17.6 \pm 2.5$ ) and panic attacks (mean  $\pm$  SD =  $7.0 \pm 6.4$  per week). None was significantly depressed at the time of study (score less than 8 on the Hamilton Rating Scale for Depression).

Blood samples were collected hourly from 10:00 p.m. to 8:00 a.m. by means of an indwelling needle

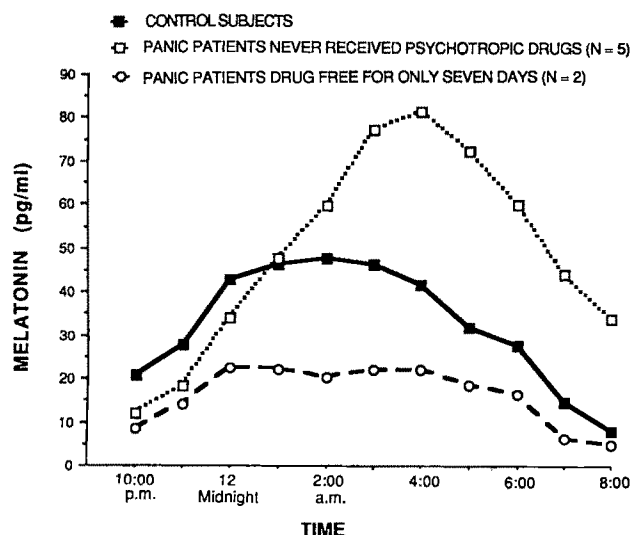
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Received May 23, 1989; revision received Sept. 8, 1989; accepted Sept. 26, 1989. From the Department of Psychiatry, University of Melbourne; the Psychoendocrine Research Unit, Austin Hospital; and the Department of Psychology and the Brain Behaviour Research Institute, Latrobe University, Bundoora, Victoria, Australia. Address reprint requests to Dr. McIntyre, Department of Psychiatry, University of Melbourne and Austin Hospital, Heidelberg, Victoria 3084, Australia.

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**FIGURE 1. Nocturnal Plasma Melatonin Concentrations in Patients With Panic Disorder and in Control Subjects**



placed in a forearm vein. The vein was maintained by using a heparin-lock system. Each patient and control subject came to the hospital on the night of investigation and was placed in a room with a background light intensity less than 10 lux from 9:00 p.m. to 8:00 a.m. the following day. Subjects were permitted to watch television, talk, or sleep, as desired. Blood was centrifuged within 1 hour of collection, and plasma was collected and stored at  $-20^{\circ}\text{C}$  until analysis. All samples were collected during the same time of year, from early November through December (late spring to early summer in Australia). Sunset at this time of year is about 7:50 p.m. to 8:45 p.m. and sunrise about 6:00 a.m. to 6:15 a.m.

The concentration of melatonin in plasma was measured by the radioimmunoassay procedure developed by Fraser et al. (15). Antiserum was purchased from Guildhay (Surrey, United Kingdom), [ $^3\text{H}$ ]melatonin from New England Nuclear (Melbourne, Australia), and other chemicals of analytical grade from Sigma (St. Louis, Mo.). Intra-assay and interassay accuracy and precision were within acceptable levels. Within the concentration range of 5–500 pg/ml, variation in precision was below 13%. Similarly, variation in accuracy (intra-assay and interassay) was less than 15% over the same concentration range.

## RESULTS

The overnight profiles of melatonin production for the control subjects and the patients are shown in figure 1. The patients were divided into two groups: those who had never received psychotropic medication ( $N=5$ ) and those who had been drug free for 7 days after withdrawal from alprazolam ( $N=2$ ). For statis-

tical analyses, data from the two patients who had been withdrawn from alprazolam were not used. All statistics, therefore, refer to the patients who had never received psychotropic drugs ( $N=5$ ) compared with the control subjects ( $N=8$ ).

A two-way analysis of variance (unweighted means) (16) between group (control versus patient) and time (10:00 p.m. to 8:00 a.m.) was performed on the melatonin concentrations. There was no significant group effect ( $F=3.57$ ,  $df=1, 11$ ,  $p=0.09$ ), but there was a significant effect of time ( $F=7.57$ ,  $df=10, 110$ ,  $p=0.0001$ ) and a significant interaction ( $F=2.88$ ,  $df=10, 110$ ,  $p=0.003$ ). The significant interaction allowed the use of a simple main effects analysis, and this showed that the differences in melatonin between the control and the unmedicated patient groups were significant ( $p<0.05$ ) at the following times: 4:00, 5:00, 6:00, and 7:00 a.m. ( $p=0.03$ ,  $p=0.005$ ,  $p=0.01$ , and  $p=0.04$ , respectively). The difference in the 8:00 a.m. values was almost significant ( $p=0.08$ ). Therefore, there was a marked increase in melatonin concentration in the unmedicated patient group in the second half of the night. This finding can be interpreted as meaning that the amplitude of the melatonin rhythms differed between the two groups. However, while it cannot be demonstrated statistically, the data are also consistent with the interpretation that there was a difference in phase between the two groups, as well as a difference in amplitude; the unmedicated patients' melatonin curve appeared to be phase delayed compared to that of the control group. The 10:00 p.m., 11:00 p.m., and midnight melatonin concentrations of the unmedicated patients were lower than those of the control group, while the 6:00, 7:00, and 8:00 a.m. concentrations remained higher, suggesting a shift to the right. However, without further measures being taken under a dim light condition at 9:00, 10:00, and perhaps 11:00 a.m., one cannot definitely state that a phase delay occurred in the unmedicated patients.

## DISCUSSION

The finding of significantly higher melatonin concentrations in the unmedicated panic patients than in the healthy control subjects was an unexpected result, because we had found lower levels in preliminary studies (12, 13). However, as discussed earlier, in the preliminary studies blood samples were not taken throughout the night, and consequently we may have missed the later increase in melatonin concentrations. Also, the patients in those previous studies were taking medication. Lewy et al. (10) have reported higher nocturnal melatonin in bipolar patients during the manic phase. Perhaps the overactivity during mania (hypomania) has effects on the pineal gland similar to those of the anxiety and panic experienced by panic patients. A correlate may be seen in studies showing that intense stress in animals can increase daytime pineal melatonin

synthesis (17). Also, there are reports that intense exercise can increase daytime melatonin in humans (18).

Alternatively, endogenous melatonin may be produced at higher concentrations by the body in an attempt to stabilize the panic patient. Exogenous melatonin administered in pharmacological doses has been shown, for example, to produce some sedation in normal control subjects (19, 20). It has been proposed that melatonin may induce sleepiness, decrease alertness, and slow reaction time, perhaps sensitizing the brain to sleep-inducing factors (21).

Although requiring confirmation in a larger sample of patients, results from these experiments suggest that patients with panic disorder have altered melatonin rhythms and peak concentrations of melatonin. However, the possibility that there is a phase delay of the circadian pacemaker in panic patients should not be overlooked. Such a delay would give the appearance of decreased melatonin production during the early hours of melatonin synthesis (i.e., up to midnight). This would also explain the later peak observed in the patients in the present study. Their melatonin peak was at 4:00 a.m., compared with 2:00 a.m. in the control subjects. Healthy individuals have previously been shown to exhibit peak levels at about 2:00 a.m. (1, 2). This finding may indicate that panic patients who have a phase instability or dysregulation would benefit from morning exposure to bright artificial light. As shown in patients with seasonal affective disorder, morning light can phase-advance circadian rhythms by suppressing melatonin (22) and thus can improve mood in most patients (23).

The present investigation substantiates our previous reports of decreased melatonin concentrations in patients with panic disorder who were taking medication (12, 13). In the present study, the two panic patients who had been drug free for only 7 days after withdrawal from alprazolam had very low melatonin levels. We now know that alprazolam can suppress nocturnal plasma melatonin levels (14). Most patients previously studied were receiving benzodiazepine medication at the time of investigation. This suggests that the effect of alprazolam on melatonin production is still evident 7 days after the last dose. This hypothesis obviously requires further evaluation of drug effects on pineal function and highlights the importance of suitable drug-free periods before patients are studied.

Finally, it is interesting to note that alprazolam has recently been reported to be extremely effective against seasonal affective disorder (unpublished 1989 paper by M.H. Teichler et al.), and the consensus of opinion is that in patients with this disorder, the melatonin rhythm is phase delayed (23). It is therefore possible that since apparently 72% of patients with seasonal affective disorder suffer from anxiety as part of their mood disturbance (24), similar biochemical mechanisms in the brain are responsible for this aspect of the disorder in patients with seasonal affective disorder and in panic patients.

## REFERENCES

1. Arendt J, Wetterberg L, Heyden T, et al: Radioimmunoassay of melatonin: human serum and cerebrospinal fluid. *Horm Res* 1977; 8:65-75
2. Arendt J, Hampton S, English J, et al: 24-hour profiles of melatonin, cortisol, insulin, C-peptide and GIP following a meal and subsequent fasting. *Clin Endocrinol (Oxf)* 1982; 16:89-95
3. Terman M, Terman J, Quitkin F, et al: Response of the melatonin cycle to phototherapy for seasonal affective disorder. *J Neural Transm* 1988; 72:147-165
4. Mendlewicz J, Linkowski P, Branchey L, et al: Abnormal 24-hour pattern of melatonin secretion in depression (letter). *Lancet* 1979; 2:1362
5. Wetterberg L, Beck-Friis J, Aperia B, et al: Melatonin/cortisol ratio in depression (letter). *Lancet* 1979; 2:1361
6. Wirz-Justice A, Arendt J: Diurnal, menstrual cycle and seasonal indole rhythms in man and their modification in affective disorders, in *Biological Psychiatry Today: Proceedings of the 2nd World Congress on Biological Psychiatry*. Edited by Obiols J, Ballus G, Gonzales-Monclus E. Amsterdam, Elsevier/North Holland, 1979
7. Brown R, Kocsis JH, Caroff S, et al: Differences in nocturnal melatonin secretion between melancholic depressed patients and control subjects. *Am J Psychiatry* 1985; 142:811-816
8. Beck-Friis J, Kjellman B, Aperia B, et al: Serum melatonin in relation to clinical variables in patients with major depressive disorders: a hypothesis of a low melatonin syndrome. *Acta Psychiatr Scand* 1985; 71:319-330
9. McIntyre I, Judd F, Norman T, et al: Plasma melatonin concentrations in depression. *Aust NZ J Psychiatry* 1986; 20:381-383
10. Lewy A, Wehr T, Gold P, et al: Plasma melatonin in manic depressive illness, in *Catecholamines: Basic and Clinical Frontiers*, vol 2. Edited by Usdin E, Kopin I, Barchas J. New York, Pergamon Press, 1979
11. Judd F, Norman T, Burrows G, et al: The dexamethasone suppression test in panic disorder. *Pharmacopsychiatry* 1987; 20:99-101
12. McIntyre I, Marriott P, Jeffreys D, et al: Reduced plasma melatonin in panic disorder. *Biol Psychiatry* 1986; 21:1438-1439
13. McIntyre I, Norman T, Marriott P, et al: The pineal hormone melatonin in panic disorder. *J Affective Disord* 1987; 12:203-206
14. McIntyre I, Burrows G, Norman T: Suppression of plasma melatonin by a single dose of the benzodiazepine alprazolam in humans. *Biol Psychiatry* 1988; 24:105-108
15. Fraser S, Cowen P, Franklin U, et al: A direct radioimmunoassay for melatonin. *Clin Chem* 1983; 29:396-399
16. Kirk RE: *Experimental Design: Procedures for the Behavioral Sciences*. Monterey, Calif, Brooks/Cole, 1982
17. Oxenkrug G, McIntyre I: Stress-induced synthesis of melatonin: possible involvement of the endogenous inhibitor (tribulin). *Life Sci* 1985; 37:1743-1746
18. L'Hermite-Baleriaux M, Casteels S, De Meirck K, et al: Running increases melatonin, in *Melatonin in Humans: Proceedings of the First International Conference on Melatonin in Humans*, Vienna, Austria, Nov 1985
19. Lieberman H, Waldhausen F, Garfield G, et al: The effects of melatonin on human mood and performance. *Brain Res* 1984; 323:201-207
20. Arendt J, Borbely A, Frany C, et al: The effects of chronic, small doses of melatonin given in the late afternoon on fatigue in man: a preliminary study. *Neurosci Lett* 1984; 45:317-321
21. Wurtman RJ, Wurtman JJ: Carbohydrates and depression. *Sci Am* 1989; 260:50-57
22. Lewy A, Sack R, Singer C: Immediate and delayed effects of bright light on human melatonin production: shifting dawn and dusk shifts the dim light melatonin onset (DLMO). *Ann NY Acad Sci* 1985; 453:253-259
23. Lewy A, Sack R, Miller S, et al: Antidepressant and circadian phase-shifting effects of light. *Science* 1987; 235:352-354
24. Rosenthal NE, Sack DA, Gillin JC, et al: Seasonal affective disorder. *Arch Gen Psychiatry* 1984; 41:72-80



# Relationship Between Utilization of Mental Health and Medical Services in a VA Hospital

Phillip M. Massad, Ph.D., Alan N. West, Ph.D., and Matthew J. Friedman, M.D., Ph.D.

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*Previous research has demonstrated a reduction in utilization of medical services following the initiation of psychiatric services for certain patients. This phenomenon has been called the offset effect. The authors investigated the offset effect in a Veterans Administration medical center setting. They found that the offset effect emerged only for patients who had high rates of use of medical services who received mental health services for 1 year or less. They discuss factors related to higher rates of medical care utilization as well as important differences between the present and previous research that require further study.*

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In medical settings where the cost of patients' care is based on a fee-for-service or prepaid group insurance arrangement, the initiation of mental health services has often correlated with a reduction in the use of medical services (1-4). One study (4), for example, reported a decline in medical service utilization among patients with high rates of use of medical services in the year after they started psychotherapy. The relationship between the use of psychiatric services and a reduction in use and cost of medical services has been called the offset effect (3).

The influence of psychiatric treatment on medical service utilization in a setting that requires no financial remuneration has received scant attention. This topic seems particularly important in establishing public policy regarding the provision of mental health services in settings where medical services are provided at no or low cost. Most patients treated at Veterans Administration (VA) medical centers receive free mental health and medical services. To our knowledge, however, only one study (5) has examined the offset effect in a VA hospital, and this study lacked a nonpsychiatric control group from which to draw comparisons. One report (6) suggested that, contrary to the offset

effect, patients with high rates of use of VA mental health services also have high rates of use of medical services (6). Therefore, the relationship between utilization of VA mental health and VA medical services needs clarification.

If there were an offset effect in a VA hospital, the number of medical visits made by psychiatric patients would be expected to be less than those made by nonpsychiatric patients. We tested this hypothesis in the investigation reported here.

## METHOD

The subjects in the study were patients of a VA hospital serving Vermont and western and northern New Hampshire. The records of veterans enrolled in medical clinics before 1985 or starting in 1985 through 1987 were examined. We identified 145 patients as having entered VA psychiatric treatment for the first time in 1986. Another group of 145 patients who had no 1986 psychiatric appointments served as a control group. This nonpsychiatric group was matched to the psychiatric sample in age and distance from the hospital based on their county of residence. The mean  $\pm$  SD age of the patients was  $53 \pm 13.26$  years.

The dependent variable was the total number of outpatient medical visits, excluding diagnostic procedures (X-ray or CT scan, for example) and surgical appointments, made by each patient in 1985, 1986, and 1987. The independent variable was whether patients were enrolled in an outpatient mental health clinic for the first time in 1986. The mean number of 1986 mental health visits for the psychiatric group was  $3.97 \pm 4.20$  visits.

## RESULTS

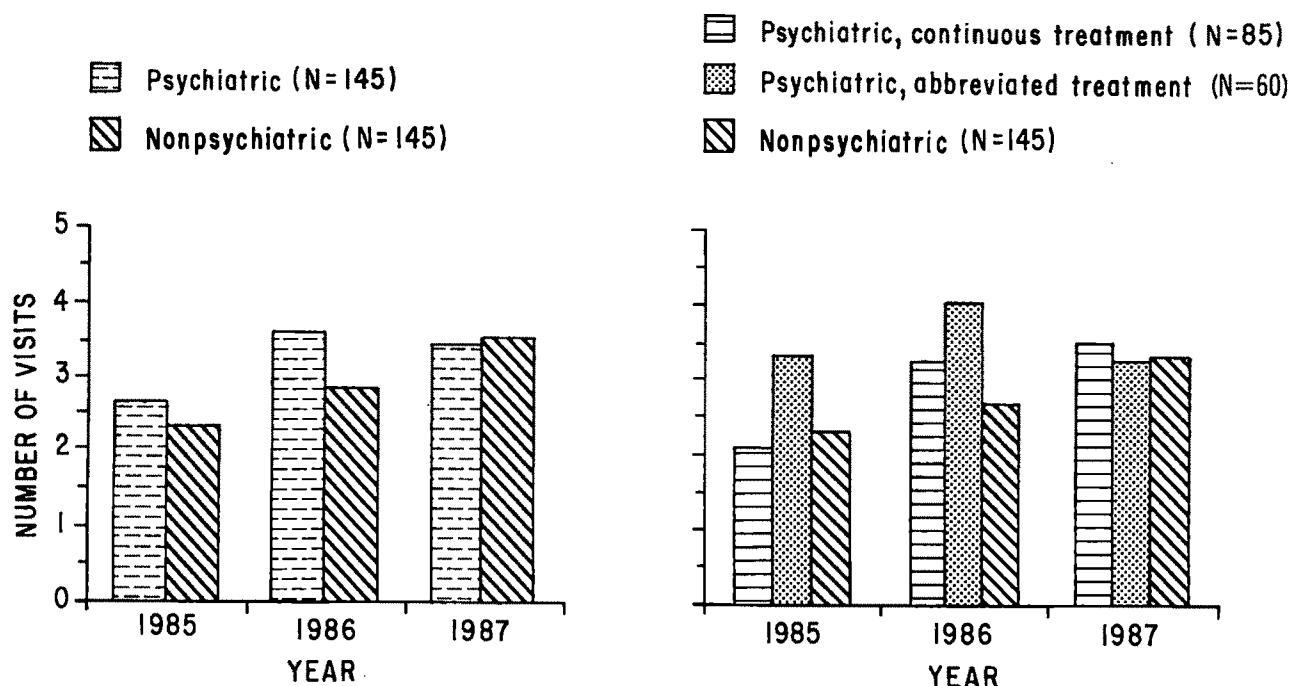
The mean number of annual outpatient medical visits for each group is shown in figure 1. Analysis of variance (ANOVA) revealed a significant main effect for Year ( $F=14.61$ ,  $df=2$ ,  $576$ ,  $p<0.01$ ) and a marginally significant Group by Year interaction ( $F=2.60$ ,  $df=2$ ,  $576$ ,  $p<0.10$ ). The Group main effect was not significant. Tukey's test revealed a significant increase

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Received March 2, 1989; revision received Sept. 12, 1989; accepted Oct. 12, 1989. From the Psychiatry Service, VA Medical Center, White River Junction, Vt., and the Departments of Psychiatry and Pharmacology, Dartmouth Medical School, Hanover, N.H. Address reprint requests to Dr. Massad, Psychiatry Services, VA Medical Center, White River Junction, VT 05001.

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FIGURE 1. Mean Number of Annual Outpatient Medical Visits Across Three Years by VA Patients Given Continuous or Abbreviated Psychiatric Care or Nonpsychiatric Medical Care



in medical visits from 1985 to 1986 for both groups combined ( $p < 0.05$ ).

A subsequent analysis was conducted to assess a more specific question: Was the impact of psychiatric care on medical utilization different for patients who received abbreviated psychiatric care versus those who received continuing psychiatric care? We classified the psychiatric patients into those who received psychiatric care only in 1986 (abbreviated care) ( $N=60$ ) and those who received psychiatric care in 1986 and 1987 (continuing care) ( $N=85$ ). The duration of psychiatric treatment ranged from 1 to 12 months for the abbreviated psychiatric care group and from 13 to 24 months for the continuing psychiatric care group. The medical visit data were then reanalyzed by a Group (nonpsychiatric medical care, abbreviated psychiatric care, or continuing psychiatric care) by Year (1985, 1986, or 1987) ANOVA. Means for the different cells of this analysis are shown in figure 1.

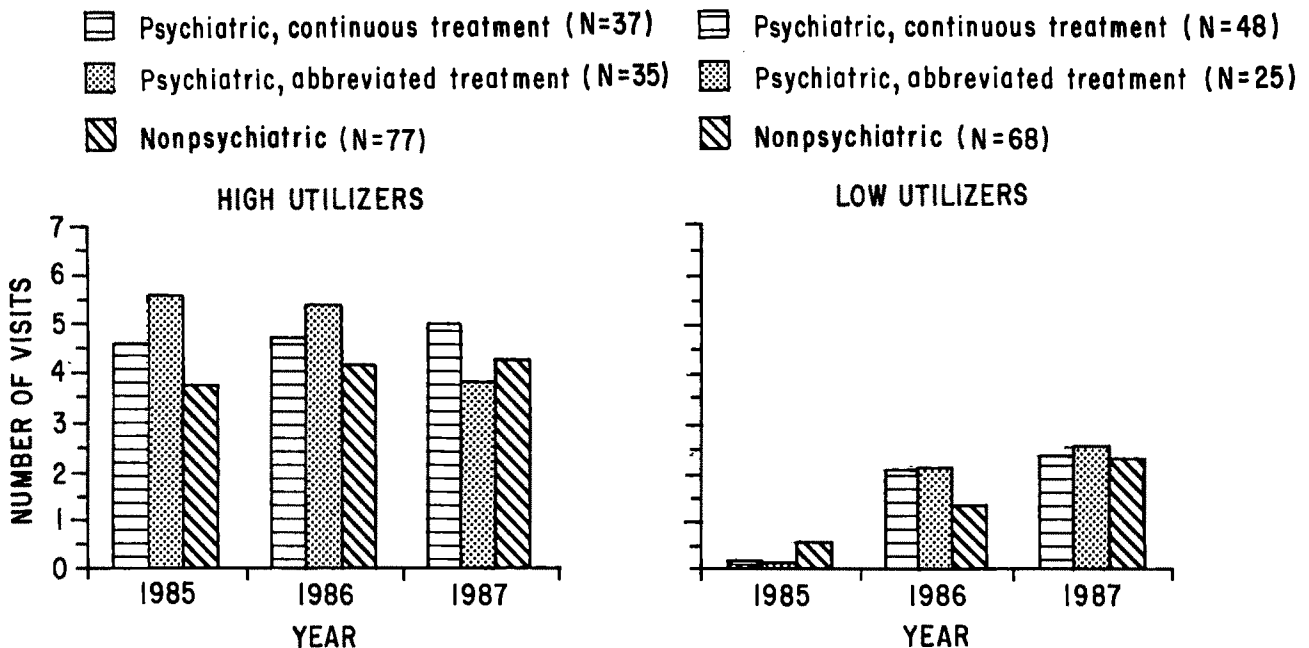
The analysis revealed a significant main effect for Year ( $F=11.17$ ,  $df=2, 574$ ,  $p < 0.01$ ) as well as a Group by Year interaction ( $F=3.65$ ,  $df=4, 574$ ,  $p < 0.01$ ). The main effect for Group was not significant. Tukey's test showed that during 1985, the psychiatric patients in the abbreviated care group had significantly more medical visits than either the psychiatric patients in the continuing care group or the nonpsychiatric control subjects ( $p < 0.05$ ). On the other hand, continuing psychiatric patients were unique in showing a significant increase in medical utilization from 1985 to 1986 ( $p < 0.05$ , Tukey's test). Medical utilization during 1986 was significantly greater for psychiatric patients in the abbreviated care group than for the nonpsychiatric control subjects ( $p < 0.05$ , Tukey's test). The significant effect

for Year resulted from an overall mean  $\pm$  SD increase in visits from 1985 ( $2.44 \pm 3.05$ ) to 1986 ( $3.11 \pm 3.47$ ), collapsed across groups ( $p < 0.05$ ). No other comparisons, including 1987, were significant.

Because classification of psychiatric patients into different categories other than the original groups violated the matched-control design, one-way ANOVA and chi-square analyses were conducted to examine differences for age and county of residence, respectively. The same analyses were conducted for group categories described below. No significant differences were found.

Because our analyses uncovered no apparent offset effect for the psychiatric groups, we conducted ancillary analyses. We noted that the mean total number of medical visits in the present study (3.2 visits) was somewhat lower than that of a previous study demonstrating an offset effect (4.3 visits) (4). Therefore, it seemed tenable that the effect of psychiatric care on medical utilization might depend on whether patients originally had high or low rates of use of medical services. To examine this possibility, the psychiatric and nonpsychiatric patients were divided into those with high or low rates of use of medical services based on a median split of 1985 medical visits: 37 patients received continuous psychiatric treatment and had high rates of use; 35 patients received abbreviated psychiatric care and had high rates of use; 77 patients received nonpsychiatric medical care and had high rates of use; 48 patients received continuous psychiatric care and had low rates of use; 25 patients received abbreviated psychiatric treatment and had low rates of use; and 68 patients received nonpsychiatric medical care and had low rates of use. Since the 1985 data were

FIGURE 2. Mean Number of Annual Outpatient Medical Visits Across Three Years by VA Patients With High or Low Rates of Use of Medical Services Who Were Given Continuous or Abbreviated Psychiatric Care or Nonpsychiatric Medical Care



used to classify the subjects, only 1986 and 1987 medical visits were analyzed through two Group (continuing psychiatric care, abbreviated psychiatric care, or nonpsychiatric medical care) by Year (1986 and 1987) repeated-measures ANOVAs: one for patients with initially high rates of medical use and another for patients with initially low rates of medical use.

The annual mean numbers of medical visits for patients with high rates of use are shown in figure 2; ANOVA revealed a significant Group by Year interaction ( $F=4.11$ ,  $df=2, 146$ ,  $p<0.05$ ) and no significant main effects. Tukey's tests indicated that the abbreviated psychiatric care group of patients with high rates of use had significantly fewer 1987 medical visits than 1986 appointments (see figure 2) ( $p<0.05$ ). A one-way ANOVA revealed that the groups differed for 1985 visits ( $F=4.34$ ,  $df=2, 146$ ,  $p<0.05$ ). Tukey's tests showed that the abbreviated psychiatric care group of patients with high rates of use had significantly more 1985 medical visits than the continuing psychiatric care and nonpsychiatric groups of patients with high rates of use ( $p<0.05$ ). Thus, patients who initially had high rates of use of medical services who then received abbreviated psychiatric care showed a dramatic reduction in subsequent medical utilization.

For patients who initially had low rates of use of medical services (see figure 2), ANOVA of medical visits revealed a significant effect for Year only ( $F=5.24$ ,  $df=1, 138$ ,  $p<0.05$ ) when collapsed across groups (mean  $\pm$  SD =  $1.67 \pm 2.32$  in 1986;  $2.32 \pm 2.68$  in 1987). In addition, a one-way ANOVA on 1985 data revealed differences among the groups ( $F=15.09$ ,  $df=2, 138$ ,

$p<0.01$ ). Tukey's tests showed that the nonpsychiatric patients who initially had low rates of use of medical services had significantly more 1985 visits than the two psychiatric groups ( $p<0.05$ ).

Medical progress notes were examined to classify patients with respect to their predominant medical complaints. Medical problems were classified as audiological, cardiovascular, dermatological, nonspecific (colds and sore throats, for example), gastrointestinal, neurological, ophthalmological, orthopedic, podiatric, rheumatological, urological, or hematological. The four categories constituting the largest percentage of medical problems were identical for both psychiatric and nonpsychiatric groups: 55 (38%) of the psychiatric and 81 (56%) of the nonpsychiatric patients had nonspecific problems; 38 (26%) of the psychiatric and 26 (18%) of the nonpsychiatric patients had gastrointestinal problems; 28 (19%) of the psychiatric and 30 (21%) of the nonpsychiatric patients had orthopedic problems; and 23 (16%) of the psychiatric and 17 (12%) of the nonpsychiatric patients had cardiovascular problems (most patients had more than one type of problem). Chi-square analyses revealed that the psychiatric and nonpsychiatric groups differed only for nonspecific medical complaints ( $\chi^2=6.50$ ,  $df=2$ ,  $p<0.05$ ). This finding was consistent regardless of group comparisons (i.e., abbreviated psychiatric care, continuing psychiatric care, or nonpsychiatric care patients with high or low rates of use of medical services). Therefore, the statistics for these groups are not reported.

In regard to psychiatric issues, patients' records were examined to identify the type of psychiatric problems



they were experiencing at the time mental health services were initiated. Chi-square analyses were conducted to test whether groups differed in the proportion of patients belonging to various diagnostic categories. There were no reliable differences for any of the following: adjustment disorders, anxiety disorders, depression, alcohol abuse, marital problems, personality disorders, posttraumatic stress disorder (PTSD), psychosis, or bipolar disorders. In addition, psychiatric groups were examined for differences across symptoms noted in patients' charts such as anger, anxiety, depression, pain, sexual dysfunction, and stress. The only difference was for both continuing care and abbreviated care patients with high rates of use to be more frequently characterized as having stress than were their counterparts with low rates of use ( $\chi^2=5.00$ ,  $df=1$ ,  $p<0.05$ ).

Groups were then examined to see whether they differed as to the type of service provided (i.e., diagnostic evaluation, medication maintenance review, or other mental health treatment such as behavioral therapy, psychotherapy, or alcohol counseling). Group differences were found only for medication maintenance review. Specifically, a chi-square analysis revealed that more continuing psychiatric care patients with high rates of use received medication maintenance review than would be expected ( $\chi^2=9.16$ ,  $df=1$ ,  $p<0.01$ ). This was not true for the abbreviated psychiatric care patients with high or low rates of use or the continuing psychiatric care patients with low rates of use. This finding would suggest that patients with more chronic illness (i.e., those who received more treatment over time) were more likely than other patients to receive medication.

In a subsidiary analysis, each psychiatric group was divided into patients who received medication only, medication and other mental health treatment, or mental health treatment alone to determine whether these subgroups differed in terms of diagnosis. The only significant finding was that, among the continuing psychiatric care patients with high rates of medical service use, those who received mental health treatment alone were more likely to have a diagnosis of personality disorder ( $\chi^2=37.00$ ,  $df=2$ ,  $p<0.01$ ). Thus, although most of the continuing psychiatric care patients with high rates of medical service use received medication reviews, a subset received no medication; rather, they had personality disorders and received mental health treatment alone.

Finally, because older patients tend to require more continuous health care than younger patients and the patients in our sample were relatively older than the patients in previous offset studies, we examined the effect of age relative to diagnosis or symptom, type of service rendered, and psychiatric group (continuing or abbreviated psychiatric care patients with high or low rates of use). For diagnosis or symptom, the only significant finding was that individuals diagnosed as having PTSD tended to be younger ( $41\pm7$  years) than

patients with other diagnoses ( $52.62\pm13.32$  years) ( $t=9.24$ ,  $df=143$ ,  $p<0.01$ ), but we should add that there were only three individuals diagnosed as having PTSD. There was no age difference for patients receiving the different types of services. For psychiatric groups, there was an age difference, collapsed across psychiatric condition (i.e., continuous and abbreviated care), between patients with high and low rates of use. That is, not surprisingly, patients with high rates of use of medical services, as previously defined, were significantly older ( $56.26\pm13.86$  years) than patients with low rates of use ( $48.56\pm11.56$ ) ( $F=13.28$ ,  $df=1$ ,  $141$ ,  $p<0.01$ ).

## DISCUSSION

Our results suggest that the introduction of psychiatric care to medical outpatients in a publicly funded VA hospital may reduce subsequent medical utilization. This offset effect, however, emerged only for patients who were initially identified as having high rates of use of medical services and who received abbreviated rather than continuous psychiatric care. The failure to observe an offset effect among patients who were initially identified as having low rates of use of medical services was not surprising because the initial levels were sufficiently low to make further reductions unlikely.

The offset effect emerged only for patients with high rates of use of medical services who received abbreviated mental health treatment (lasting for 1 year or less). The offset effect was not manifested by patients with high rates of use of medical services who received continuing psychiatric care. The continuing psychiatric care group with high rates of use also differed from other patients in that they were more likely to be seen regularly for medication maintenance review. The implication is that continuing psychiatric care patients with high rates of use were more likely to suffer from chronic and more severe psychiatric problems than the other groups regardless of diagnosis or symptom. Apparently, continuing mental health care had little impact on the need for medical services of the continuing psychiatric care patients with high rates of use of medical services. For abbreviated psychiatric care patients with high rates of use of medical services, on the other hand, medical demand seems to have been more strongly associated with psychiatric complaints. When their mental health needs were addressed, their use of medical services declined.

## REFERENCES

1. Goldensohn SS, Fink R: Mental health services for Medicaid enrollees in a prepaid group practice plan. *Am J Psychiatry* 1979; 136:160-164
2. Norfleet MA, Burnell GM: Utilization of medical services by

- psychiatric patients. *Hosp Community Psychiatry* 1981; 32:198–200
3. Shemo PD: Cost-effectiveness of providing mental health services: the offset effect. *Int J Psychiatry Med* 1985; 15:19–30
  4. Kessler LG, Steinwachs DM, Hankin JR: Episodes of psychiatric care and medical utilization. *Med Care* 1982; 20:1209–1221
  5. Comstock BS, Kamilar SM, Thornby JI, et al: Crisis treatment in a day hospital: impact on medical care-seeking. *Psychiatr Clin North Am* 1985; 8:483–500
  6. Friedman MJ, West AN: Current need versus treatment history as predictors of use of outpatient psychiatric care. *Am J Psychiatry* 1987; 144:355–357

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# The Borderline Diagnosis in Adolescents: Symptoms and Developmental History

Pamela S. Ludolph, Ph.D., Drew Westen, Ph.D., Barbara Misle, B.A.,  
Anne Jackson, M.A., Jean Wixom, Ph.D., and F. Charles Wiss, M.A.

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*Adult criteria for borderline personality disorder distinguished a group of 27 inpatient adolescent girls from 23 nonborderline inpatient female comparison subjects. The two groups were compared on retrospectively assessed variables measuring psychological, familial, and constitutional factors. Variables most likely to predict borderline personality disorder included history of disrupted attachments, maternal neglect, maternal rejection, grossly inappropriate parental behavior, number of mother and father surrogates, physical abuse, and sexual abuse. Families of borderline adolescents were chronically disrupted, particularly during the patients' early childhoods. The traumatic childhood experiences of the borderline adolescents were similar to those of adults with borderline personality disorder in recent studies.*

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The borderline diagnosis in children and adolescents has been commonly used by clinicians but has not been clearly defined and understood. Historically, the diagnosis was first used to delineate a group of atypical children on the "border" between psychosis and neurosis (1, 2), much as adult patients were first classified. More recently, attempts have been made to describe a borderline disorder in children according to uniform diagnostic criteria, most often parallel to adult borderline personality disorder (3, 4, and *DSM-III-R*). For instance, Bradley (4) found that 14 child and adolescent patients could be diagnosed by the

Gunderson and Singer criteria (5) and that these borderline subjects were distinguished from psychiatric control subjects by histories of significantly more separation from their mothers before age 5.

Greenman et al. (6) examined the borderline personality disorder diagnosis in children 6-12 years old. They reviewed the charts of 86 hospitalized children and found that adult criteria adapted from the Diagnostic Interview for Borderlines (DIB) (7) could identify a group of children with many features typically attributed to the borderline child. Subjects identified as borderline were then compared to nonborderline psychiatric control subjects on a group of variables selected because of their presumed association with the borderline syndrome. Overall, few differences were found, raising questions about the meaning of the borderline diagnosis in early childhood and its relation to criteria for adult borderline personality disorder. Although this study was exploratory and thus had certain methodological limitations (8, 9), such as using DIB scores as both dependent and independent variables, it nevertheless provided an initial empirical examination of the borderline diagnosis in children.

The present study examined borderline personality disorder in adolescent girls. We first distinguished adolescent patients according to adult DIB criteria (10) and then compared the borderline patients with nonborderline psychiatric comparison subjects on a number of independent variables. We selected these variables to address controversies in the literature on the developmental antecedents of borderline personality disorder. Some theorists, for instance, have stressed the importance of a highly disturbed relationship with the mother (11, 12), with special emphasis on the role of significant separations from the mother (4, 13). Psychoanalytic theorists have long emphasized the etiological importance of deficits and conflicts involving separation and loss, especially during the preoedipal years (11, 14). More generally, clinicians have often noted the manifest turmoil in borderline patients' families of origin. Among the factors often implicated are severe trauma and abuse, incest, loss, multiple caretakers, violence, and alcoholism (13, 15-18).

Other data have pointed to the importance of constitutional factors. Although there are presently few data supporting a link between borderline personality

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disorder and either bipolar disorder or schizophrenia (5), there is some support for a link with the unipolar affective disorders (19, 20). Family pedigree studies have also suggested an association between borderline personality disorder and certain other personality disorders, notably antisocial, narcissistic, and histrionic (21, 22).

In the present study, then, borderline adolescents were compared with nonborderline psychiatric comparison subjects to test hypotheses about separation and loss; disruption in the relationships with the mother and father; incest, abuse, and other indicators of severe financial dysfunction; and selected indices of family psychopathology. The study closely parallels the Greenman et al. study (6), except that the subjects were defined prospectively, were compared only on nondiagnostic criteria, and were adolescents rather than children.

## METHOD

The data were collected as part of an ongoing study of the life experiences and interpersonal functioning of borderline adolescent girls (23–25). The subjects were 50 female adolescents psychiatrically hospitalized at a major medical center. Adolescent girls were studied because of the preponderance of females in the borderline population. Patients with chronic psychosis, evidence of gross neuropathology, IQ below 70, or medical problems that would complicate diagnosis or psychological testing were excluded from the study. Potential subjects who consented (and whose parents consented) were given the DIB (7), which had been modified slightly for administration to adolescents, largely to discern patterns of interpersonal functioning in subjects who might not yet have developed an intimate relationship outside the biological family. As in other research using the DIB, patients were considered to meet the criteria for borderline personality disorder if they had DIB scores greater than or equal to 7. Patients had to have DIB scores less than or equal to 5 to qualify as psychiatric comparison subjects. Subjects who had scores of 6 were excluded, as decided in advance, so that the diagnostic differences between the two study groups would be clearer.

During 1983 and 1984, consecutive patients were administered the DIB by interviewers who had achieved an interrater reliability of 0.80 (kappa) on diagnosis. In order to fill the borderline group more expeditiously and to obtain appropriate comparison subjects, from 1985 to 1987 we targeted potential subjects who met at least four of the *DSM-III* criteria for borderline personality disorder, the criteria for anorexia nervosa, or two criteria for major depression or dysthymic disorder on admission. Two interviewers with previously established reliability on the DIB (26) trained additional interviewers, who achieved perfect agreement on DIB diagnoses with a sample of consecutive taped interviews and came within 1 scaled point

of the criterion coder's rating on every section and final score. The nonborderline psychiatric comparison subjects received a number of *DSM-III* discharge diagnoses—primarily, affective disorders, anorexia, and nonborderline personality disorders. Potential comparison subjects who received primary or secondary *DSM-III* diagnoses of borderline personality disorder on discharge were excluded, as decided in advance, again to avoid overlap of groups.

In order to increase further the size of the comparison group, we added another six subjects on the basis of DIB scores determined by chart review, which has been shown to be a reliable way of diagnosing borderline personality disorder in adults (26) and children (6). Potential comparison subjects were selected by a computer search of female inpatients between the ages of 14 and 17, hospitalized from 1985 to 1988, with discharge diagnoses of affective disorders or eating disorders. Potential comparison subjects were excluded if they had primary or secondary diagnoses of borderline personality disorder, schizophrenia, conduct disorder, or serious medical illness. Two of the authors (P.S.L. and D.W.) read admission information, discharge summaries, and the first 2 weeks' progress notes in the patients' charts and assigned scores on the DIB. Of 10 potential comparison subjects, one was excluded because of medical illness, two received scores of 6 and thus were excluded, and the six with scores of 5 or below were included in the nonborderline sample. To ensure continued reliability (since the raters knew that the purpose of the chart review DIBs was to obtain additional comparison subjects), one potential subject who had a primary *DSM-III* diagnosis of borderline personality disorder was included for chart review; this subject also received a borderline diagnosis by chart review DIB, thus corroborating the reliability of that method.

Twenty-seven inpatients were diagnosed as having borderline personality disorder. The psychiatric comparison group consisted of 23 other inpatients: seven with depression, nine with eating disorders, and seven with other personality disorders. The mean age of the borderline group was 15.75 years (range=14–18 years); the psychiatric comparison group's mean age was 15.46 years (range=14–18 years).

Chart review was used to determine the presence or absence of various descriptive and etiological factors. Data in the charts had been originally collected primarily for clinical purposes, for the most part by psychiatrists, supervised psychiatric residents, and experienced social workers. In general, the available information was extensive, based on data from thorough questioning of the patient, her parent(s), other family members, and ward staff. A trained rater (B.M.), blind to patients' diagnoses, read the following parts of the charts of discharged patients: the individual therapist's summary report, the social worker's summary, the individual therapist's process notes, the case conference report, the first 2 weeks' nursing notes, the intake summary, notes from previous therapists, school reports,

**TABLE 1. Composite Risk Variables for 27 Adolescent Borderline Patients and 23 Psychiatric Comparison Subjects**

Composite Variable	Borderline Patients		Psychiatric Comparison Subjects		$t^a$ (df=48)	p
	Mean	SD	Mean	SD		
Maternal risk factors	2.93	2.01	2.09	1.54	1.63	0.05
Paternal risk factors	3.30	2.11	3.00	1.73	0.54	n.s.
Preoedipal risk factors	1.74	1.85	1.00	1.45	1.56	0.06
Latency risk factors	3.48	2.03	3.09	1.59	0.76	n.s.
Disrupted attachments	5.67	3.45	3.26	2.18	2.89	0.003

<sup>a</sup>One-tailed test.

and court reports (if available). Charts were rated for variables assessing the family history of psychopathology; childhood symptoms of the patient; a variety of traumatic events, including physical and sexual abuse; and significant separations, including death, divorce, adoption, separations from primary caretakers, and foster care history. It should be emphasized that each variable was coded as present only if there was conclusive evidence. It is therefore very likely that these data led to few false positive results and relatively more false negatives. Although the data we rated were largely factual and required little inference, a check was undertaken to ensure reliable rating. A second rater (F.C.W.) blindly rescored all variables for a small sample of the subjects; the two raters achieved perfect agreement on 89% of the scores.

## RESULTS

Twenty-one of the 29 scores on DIB statements differentiated the two groups at high levels of significance (typically,  $p=0.001$  to  $0.0001$ , one-tailed  $t$  tests,  $df=48$ ). Four of the five DIB subscale scores—impulse patterns, affect, psychosis, and interpersonal relations—also differentiated the groups at very high levels ( $p=0.0001$ ).

Table 1 presents comparisons of the borderline patients and the psychiatric comparison subjects on five composite variables of conceptual significance: number of maternal and paternal risk factors (psychiatric illness or disorder, losses, separation, and abuse); number of preoedipal risk factors (premature delivery, difficult infancy, separation or loss before age 5, and physical or sexual abuse before age 5); number of risk factors in latency (loss, separation, or abuse between ages 5 and 10; school learning problems); and number of disrupted attachments (separations and losses at any time in childhood, expulsion from the home, number of foster care placements, number of maternal and paternal surrogates). As can be seen in table 1, in these adolescents borderline personality disorder was signif-

icantly more associated with problems in the relationships with the mothers and, particularly, with disrupted attachments. There was a strong trend associating borderline personality disorder with theoretically relevant preoedipal experiences.

To protect against spurious findings stemming from multiple tests in subsequent analyses, a multivariate analysis of variance (MANOVA) was performed using the five composite variables to predict diagnostic status. Excluding paternal risk factors, the MANOVA was significant ( $F=2.87$ ,  $df=4$ ,  $45$ ,  $p=0.03$ ); since inclusion of paternal risk factors rendered the overall MANOVA nonsignificant, any specific findings with respect to paternal variables should be interpreted with caution.

Table 2 presents the childhood histories of major separations in the two groups of patients. Both groups had very high rates of early separation from parental figures. Thus, in both groups, about one-fourth of the subjects had experienced the death of one or both parents by the time they were adolescents. An even larger proportion of both groups had been separated from either their mothers or their fathers for considerable periods of time. Divorce had marked the lives of more than half the subjects in both groups, although the age of the children when the divorces occurred differed to an almost significant degree; the borderline adolescents were more likely to have experienced parental divorce early in their lives, particularly in the first 4 years.

The borderline adolescents were significantly more likely than the psychiatric comparison subjects to have been adopted. The borderline subjects also had had significantly more surrogate mothers ( $\text{mean} \pm \text{SD} = 1.00 \pm 1.04$  for the borderline patients and  $0.26 \pm 0.47$  for the psychiatric comparison subjects;  $t=3.17$ ,  $df=1$ ,  $p=0.001$ ) and surrogate fathers ( $0.85 \pm 0.99$  for the borderline patients and  $0.43 \pm 0.66$  for the comparison subjects;  $t=1.72$ ,  $df=1$ ,  $p=0.05$ ). In addition, the borderline adolescents had had a  $\text{mean} \pm \text{SD}$  of  $1.67 \pm 1.98$  foster care placements or surrogate homes each, whereas the psychiatric comparison subjects had had  $0.48 \pm 0.85$ , a highly significant difference ( $t=2.67$ ,  $df=1$ ,  $p=0.005$ ).

Table 3 shows the numbers in both groups who experienced a variety of pathogenic circumstances in their childhood family environments. The families of the borderline patients were more likely to have been involved with Protective Services than the families of the psychiatric comparison subjects. The primary caretakers of the borderline patients—usually, their mothers—had more often behaved in ways that were labeled in the chart reviews as neglectful (e.g., failure to feed, clothe, or protect the child). As we defined it, expulsion by the primary caretaker involved the child's actually being removed from the home, usually forcibly and sometimes with court involvement. It is striking that 40.7% of the borderline group had experienced such an event, compared with only 8.7% of the psychiatric comparison group.

We developed a variable called "grossly inappropri-

**TABLE 2. Major Separations and Changes in Attachment During Childhood of 27 Adolescent Borderline Patients and 23 Psychiatric Comparison Subjects**

Separation or Change	Borderline Patients <sup>a</sup>		Psychiatric Comparison Subjects <sup>a</sup>		$\chi^2$ (df=1)	p
	N	%	N	%		
Divorce	15	55.6	12	52.2	7.34 <sup>b</sup>	0.06
When child was 0–4 years old	8	29.6	2	8.7	—	—
When child was 5–10 years old	6	22.2	4	17.4	—	—
When child was 11 or older	1	3.7	6	26.1	—	—
Death						
Of parent	6	22.2	6	26.1	0.10	n.s.
Of surrogate parent	4	14.8	5	21.7	0.40	n.s.
Separation						
From mother	11	40.7	6	26.1	1.18	n.s.
From father	16	59.3	10	43.5	1.20	n.s.
Adoption	6	23.1	0	0.0	6.05	0.05
When child was younger than 3 months	2	7.7	0	0.0	2.19	n.s.
When child was older than 3 months	4	15.4	0	0.0	4.19 <sup>c</sup>	0.04

<sup>a</sup>Total Ns on which percentages are based vary slightly because of missing data on some variables for some patients.

<sup>b</sup>df=3.

<sup>c</sup>df=2.

**TABLE 3. Physical and Sexual Abuse and Other Traumatic Events in the Childhood Family Environments of 27 Adolescent Borderline Patients and 23 Psychiatric Comparison Subjects**

Traumatic Event	Borderline Patients <sup>a</sup>		Psychiatric Comparison Subjects <sup>a</sup>		$\chi^2$ (df=1)	p
	N	%	N	%		
Severe verbal fighting between parents	12	44.4	7	30.4	1.03	n.s.
Physical fighting between parents	8	29.6	5	21.7	0.40	n.s.
Involvement with Protective Services	10	37.0	3	13.0	3.71	0.05
Neglect by primary caretaker	12	44.4	4	17.4	4.18	0.04
Expulsion by primary caretaker	11	40.7	2	8.7	6.63	0.01
Grossly inappropriate parental behavior	12	44.4	2	8.7	7.87	0.005
Physical abuse	14	51.9	6	26.1	3.44	0.06
Sexual abuse	13	52.0	4	19.0	5.32	0.02

<sup>a</sup>Total Ns on which percentages are based vary slightly because of missing data on some variables for some patients.

ate parental behavior." Examples of events in this category included an adolescent girl double-dating with her father and his girlfriend and watching each other's sexual behavior; parents threatening to maim family pets; and a mother giving her borderline daughter a loaded gun, saying, "Shoot me if you hate me that much." This variable was rated as present for 44.4% of the borderline group and only 8.7% of the psychiatric control subjects, a highly significant difference (see table 3).

As we have described more fully elsewhere (23), physical abuse was more common in the families of the borderline patients, at a level that almost reached statistical significance. Sexual abuse was much more common in the histories of the girls with borderline personality disorder. Fifty-two percent had been sexually abused, compared to 19% of the psychiatric comparison group (see table 3).

Table 4 presents the psychiatric histories reported for the relatives of the two groups of adolescent subjects; only information on biological relatives is re-

ported. For both groups there were very high rates of psychiatric illness in the parents, and 72% of the borderline patients and 87% of the psychiatric comparison patients had a first-degree relative with a major psychiatric illness. Depression was common in the relatives of both groups, particularly in the mothers, and drug and alcohol abuse were common, particularly in the fathers. Parental psychosis was rare in both groups. There were very high rates of criminal behavior for the fathers and first-degree relatives of both groups. There were, however, no significant differences between the groups in family history of psychiatric illness and related variables. Trends in the data supported a link between a child's borderline status and personality disorder in the mother (see table 4); this trend grew stronger ( $\chi^2=3.30$ ,  $df=1$ ,  $p<0.07$ ) when adoptive mothers were added to the group. Mothers of the borderline patients also tended to have been physically abused and to be physically abusive more often than the mothers of the psychiatric comparison subjects.

Table 5 presents relevant events and symptoms in



TABLE 4. Psychiatric Histories of the Biological Relatives of 27 Adolescent Borderline Patients and 23 Psychiatric Comparison Subjects

Psychiatric History	Relatives of Borderline Patients <sup>a</sup>		Relatives of Psychiatric Comparison Subjects <sup>a</sup>		$\chi^2$ (df=1)	p
	N	%	N	%		
Biological mothers						
Any psychiatric illness	15	60.0	11	47.8	0.72	n.s.
Depression	7	28.0	8	34.8	0.26	n.s.
Drug or alcohol abuse	7	28.0	3	13.0	1.62	n.s.
Psychosis	0	0.0	0	0.0	—	—
Psychiatric hospitalization	2	8.0	1	4.3	0.27	n.s.
Criminal behavior	2	8.0	0	0.0	1.92	n.s.
Sexually abused	3	12.0	3	13.0	0.01	n.s.
Physically abused	11	44.0	4	17.4	5.02	0.08
Personality disorder						
Borderline	2	8.0	1	4.3	0.27	n.s.
Unspecified	5	20.0	1	4.3	2.68	0.10
Abusive toward others	3	12.0	0	0.0	2.94	0.09
Biological fathers						
Any psychiatric illness	16	66.7	17	73.9	0.29	n.s.
Depression	5	20.8	3	13.0	0.50	n.s.
Drug or alcohol abuse	9	37.5	10	43.5	0.17	n.s.
Psychosis	1	4.2	2	8.7	0.40	n.s.
Psychiatric hospitalization	2	8.3	0	0.0	2.00	n.s.
Criminal behavior	5	20.8	5	21.7	0.00	n.s.
Sexually abused	0	0.0	1	4.3	1.07	n.s.
Physically abused	1	4.2	1	4.3	0.00	n.s.
Personality disorder						
Borderline	0	0.0	0	0.0	—	—
Unspecified	4	16.7	3	13.0	0.12	n.s.
Abusive toward others	11	45.8	6	26.1	1.98	n.s.
First-degree relatives						
Any psychiatric illness	18	72.0	20	87.0	1.62	n.s.
Depression	12	50.0	11	47.8	0.02	n.s.
Drug or alcohol abuse	11	45.8	11	47.8	0.02	n.s.
Psychosis	2	8.3	1	4.3	0.31	n.s.
Psychiatric hospitalization	6	25.0	2	8.7	2.21	n.s.
Criminal behavior	8	32.0	5	21.7	0.63	n.s.
Suicide attempt	8	33.3	3	13.0	2.70	0.10
Sexually abused	5	20.8	4	17.4	0.09	n.s.
Physically abused	13	52.0	6	26.1	3.36	0.07

<sup>a</sup>Total Ns on which percentages are based vary slightly because of missing data on some variables for some patients.

childhood that were not assessed by the DIB. Again, most of these variables did not distinguish the two groups of adolescent patients. Not surprisingly, the comparison group, in which approximately one-third of the subjects had eating disorders, reported a greater frequency of symptomatic anorexia. It is interesting to note, though, that the borderline group more frequently reported bulimia. Complications of birth and infancy did not distinguish the groups, but enuresis did. Sleep disorder was common in both groups, as was suicidal behavior.

A final data analysis was carried out to assess which of the specific variables might most efficiently predict borderline personality disorder. Using a logistic regression analysis, we found that nine variables predicted 89% of the diagnoses (borderline personality disorder versus the psychiatric comparison diagnoses) at a significance level of 0.0006. These variables were neglect, maternal rejection, grossly inappropriate parental behavior, parental loss, number of surrogate mothers and fathers, number of relocations, physical abuse, and sexual abuse.

## DISCUSSION

The results of this study suggest that adult criteria can be used to distinguish borderline adolescents from psychiatric comparison subjects. Borderline subjects are discriminable with the DIB, and the groups yielded by using this instrument manifest different developmental histories, coded independently of DIB diagnosis. The histories of our borderline adolescents were similar in very many respects to reports in the literature of the early development of adults with borderline personality disorder (12–18).

Our data provide strong support for the etiological significance of disrupted attachments, rejection, abuse, and general family chaos in the developmental histories of borderline adolescents. Problems in the relationship with the mother placed a child at increased risk for borderline personality disorder. The pathogenic events and relationships to which the borderline subjects had been exposed were many, various, and chronic. Although traumatic separations were common in both groups, the borderline subjects had sig-

**TABLE 5. Personal Histories of 27 Adolescent Borderline Patients and 23 Psychiatric Comparison Subjects**

Variable	Borderline Patients <sup>a</sup>		Psychiatric Comparison Subjects <sup>a</sup>		$\chi^2$ (df=1)	p
	N	%	N	%		
Premature birth	3	14.3	2	9.1	0.28	n.s.
Complicated delivery	7	33.3	4	19.0	1.11	n.s.
Difficult infant	5	19.2	3	13.6	0.27	n.s.
Encopresis	0	0.0	0	0.0	—	—
Enuresis	7	26.9	0	0.0	6.93	0.009
Anorexia	2	7.4	8	34.8	5.82	0.02
Bulimia	6	22.2	4	17.4	0.18	n.s.
Obesity	2	7.4	2	8.7	0.03	n.s.
Insomnia	14	51.9	14	60.9	0.41	n.s.
Hypersomnia	6	22.2	7	30.4	0.44	n.s.
Suicidal behavior						
Threat	26	96.3	17	73.9	5.17	0.02
Any attempt	22	81.5	10	43.5	7.79	0.005
Serious attempt	5	18.5	3	13.0	0.28	n.s.
Amnesia	4	14.8	1	4.3	1.51	n.s.
Learning problems	5	19.2	2	8.7	1.11	n.s.

<sup>a</sup>Total Ns on which percentages are based vary slightly because of missing data on some variables for some patients.

nificantly more surrogate mothers and fathers and foster care placements or surrogate homes.

Little in our findings supports the notion that borderline personality disorder is the result of a single trauma at any particular phase of development. Instead, trauma was cumulative in its effect, and traumatic events in early childhood tended especially to be associated with borderline outcome. As we have elaborated elsewhere (23), problematic attachment histories generally coexisted with, and were exacerbated by, conditions of abuse, neglect, and rejection. With few exceptions, the atmosphere in these families was stressed by sociological, biological, and psychological factors of all kinds. Although major psychiatric illness was common in the relatives of all of our subjects, differences between groups reached significance on no single variable. Such trends as there were support a link between daughters with borderline personality disorder and mothers with personality disorder of some kind.

The results of this study can be compared to those of Greenman et al.'s work on the borderline diagnosis in children (6). More DIB items (21 versus eight) discriminated borderline subjects from psychiatric comparison subjects in our adolescent sample than in the younger children studied by Greenman et al. Also, relatively few etiological variables distinguished the borderline and nonborderline groups in the Greenman et al. study, whereas a large number did so in our study.

The conclusions to be drawn from this study are limited by its methodology. First, the chart review data were retrospective. The accessibility of information obtained from the parents while the adolescent was hospitalized, however, constitutes an improvement

over similar studies of adults, in which the families of origin are usually unavailable for interview and childhood histories must be reconstructed on the basis of very long-term recall. Although direct interview would have provided useful additional information, this information alone would not necessarily have been more valid than the data obtained from multiple sources, including the patient, that were found in the charts. Also, as we have pointed out, we chose to bias chart review coding in the direction of false negatives rather than false positives, which makes some of the findings all the more striking.

Although diagnosis was standardized by administration of the DIB, sampling biases could have been introduced by the different screening criteria and different interviewers used at the beginning and the end of the study. However, paired *t* tests comparing DIB item and section scores from the two phases of data collection revealed no significant differences, suggesting that the diagnostic criteria did not substantially change. Inclusion of six comparison subjects chosen by chart review only is also unlikely to have contaminated the comparison sample because all six subjects were independently given nonborderline diagnoses by both the DIB and their primary clinicians, and there were no differences on any DIB items between this subgroup and the other comparison subjects.

The other major limitation of the study is that we studied only adolescent girls, and thus the findings may not be applicable to boys with borderline disorder. Given the considerable sex differences in the borderline diagnosis, we chose not to add an additional confounding variable in a study with small sample sizes by including four or five boys in each group.

Despite these limitations, the results are clear and internally consistent enough to support the proposition that a chaotic and traumatic early environment provides fertile ground on which borderline personality disorder can develop.

#### REFERENCES

1. Fast I, Chethik M: Some aspects of object relations in borderline children. *Int J Psychoanal* 1972; 53:479-485
2. Pine F: On the concept "borderline" in children. *Psychoanal Study Child* 1974; 29:341-368
3. Pfeffer CR, Plutchik R, Mizruchi MS: Suicidal and assaultive behavior in children: classification, measurement, and interrelations. *Am J Psychiatry* 1983; 140:154-157
4. Bradley SJ: The relationship of early maternal separation to borderline personality in children and adolescents: a pilot study. *Am J Psychiatry* 1979; 136:424-426
5. Gunderson JG, Singer MT: Defining borderline patients: an overview. *Am J Psychiatry* 1975; 132:1-10
6. Greenman DA, Gunderson JG, Cane M, et al: An examination of the borderline diagnosis in children. *Am J Psychiatry* 1986; 143:998-1003
7. Gunderson JG, Kolb JE, Austin V: The Diagnostic Interview for Borderline Patients. *Am J Psychiatry* 1981; 138:896-903
8. Gualtieri CT, Van Bourgondien ME: So-called borderline children (letter). *Am J Psychiatry* 1987; 144:832
9. Behar D, Stewart MA: The borderline diagnosis for children (letter). *Am J Psychiatry* 1987; 144:1108

10. McManus M, Lerner H, Robbins D, et al: Assessment of borderline symptomatology in hospitalized adolescents. *J Am Acad Child Psychiatry* 1984; 23:685-694
11. Masterson JF: *The Psychotherapy of the Borderline Adult: A Developmental Approach*. New York, Brunner/Mazel, 1976
12. Masterson JF, Rinsley DB: The borderline syndrome: the role of the mother in the genesis and psychic structure of the borderline personality. *Int J Psychoanal* 1975; 56:163-177
13. Soloff P, Millward J: Developmental histories of borderline patients. *Compr Psychiatry* 1983; 24:574-588
14. Mahler MS, Pine F, Bergman A: *The Psychological Birth of the Human Infant*. New York, Basic Books, 1975
15. Gunderson JG, Zanarini MC: Current overview of the borderline diagnosis. *J Clin Psychiatry* 1987; 48:5-14
16. Ogata SN, Silk KR, Goodrich S, et al: Childhood abuse and clinical symptoms in borderline personality disorder, in CME Syllabus and Proceedings Summary, 141st Annual Meeting of the American Psychiatric Association. Washington, DC, APA, 1988
17. Gunderson JG, Englund DW: Characterizing the families of borderlines. *Psychiatr Clin North Am* 1981; 4:159-168
18. Herman JL, Perry JC, van der Kolk BA: Childhood trauma in borderline personality disorder. *Am J Psychiatry* 1989; 146: 490-495
19. Akiskal HS: Sub-affective disorders: dysthymic, cyclothymic and bipolar II disorders in the "borderline" realm. *Psychiatr Clin North Am* 1981; 4:25-46
20. Klein DF: Psychopharmacology and the borderline patient, in *Borderline States in Psychiatry*. Edited by Mack J. New York, Grune & Stratton, 1975
21. Pope HG Jr, Jonas JM, Hudson JI, et al: The validity of *DSM-III* borderline personality disorder. *Arch Gen Psychiatry* 1983; 40:23-30
22. Loranger AW, Oldham JM, Tulis EH: Familial transmission of *DSM-III* borderline personality disorder. *Arch Gen Psychiatry* 1982; 39:795-799
23. Westen D, Ludolph PS, Mislé B, et al: Physical and sexual abuse in female adolescents with borderline personality disorder. *Am J Orthopsychiatry* 1990; 60:55-66
24. Westen D, Ludolph PS, Lerner H, et al: Object relations in borderline adolescents. *J Am Acad Child Adolesc Psychiatry* (in press)
25. Westen D, Ludolph P, Silk K, et al: Object relations in borderline adolescents and adults: developmental differences. *Adolesc Psychiatry* (in press)
26. Cornell DG, Silk KR, Ludolph PS, et al: Test-retest reliability of the Diagnostic Interview for Borderlines. *Arch Gen Psychiatry* 1983; 40:1307-1310



# Glucose Tolerance Testing in Women With Premenstrual Syndrome

Kirk D. Denicoff, M.D., M. Christine Hoban, M.S.W.,  
Gay N. Grover, R.N., M.S.N., and David R. Rubinow, M.D.

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*Glucose tolerance tests (GTTs) were administered to 11 women with premenstrual syndrome (PMS) to ascertain whether the patients had abnormalities of glucose tolerance, to determine whether such abnormalities were related to menstrual cycle phase, and to compare the symptoms during the GTT with the PMS symptoms experienced in the luteal phase. Two GTTs were performed for each patient, one during the late follicular phase and one during the late luteal phase. Although many patients experienced symptoms of hypoglycemia during the GTT, the hypoglycemia symptoms were not specific to the luteal phase and did not resemble the patients' PMS symptoms.*

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Symptoms associated with premenstrual syndrome (PMS) are diagnostically nonspecific; over 150 symptoms have been attributed to PMS (1, 2). Despite at least 50 years of study, a biological marker for PMS has not been identified (3). Some of the physiological symptoms associated with PMS, such as increased appetite, carbohydrate craving, and fatigue, are also symptoms of hypoglycemia. One explanation for some of the symptoms experienced by women with PMS is that abnormal changes in glucose metabolism may occur during the menstrual cycle. De Pirro et al. (4) found that insulin binding to monocytes is twice as high in the follicular phase as in the luteal phase. This finding implies that changes in glucose tolerance may be related to the menstrual cycle. The results of past studies of menstrual-cycle-related changes in glucose tolerance in normal women and in women with PMS are contradictory. Several investigators have reported changes in glucose tolerance during the menstrual cycle (5-8), while others have observed no effect of the

menstrual cycle on glucose tolerance (9-12). Most earlier studies were hampered by at least one of the following methodologic problems: failure to prospectively confirm the diagnosis of PMS in the subjects, failure to perform a sufficiently long glucose tolerance test (GTT) (some studies lasted only 2 hours), and failure to ensure an adequate carbohydrate intake before the GTT (13; this study showed that carbohydrate restriction followed by concentrated carbohydrate ingestion produces hypoglycemia in normal subjects). Because of these methodologic problems, we elected to administer GTTs to patients prospectively characterized as having PMS while carefully controlling the variables noted. We hoped in this way to document the presence of abnormalities of glucose tolerance, to determine whether these abnormalities were related to phase of the menstrual cycle, and to compare the symptoms during the GTT with the PMS symptoms customarily experienced in the luteal phase. To address these questions, two GTTs were performed on each patient, one during the late follicular phase and one during the late luteal phase.

## METHOD

All studies were done in the outpatient clinic of the National Institute of Mental Health. Eleven women with PMS were studied (mean age  $\pm$  SD =  $36.2 \pm 6.2$  years). Before the study, the timing and severity of all 11 women's mood symptoms were prospectively confirmed with daily visual analogue scale self-ratings, as described previously (14). According to these self-ratings, in at least two of three menstrual cycles each patient demonstrated a mean rating for negative mood (depression, anxiety, irritability) during the week before menstruation that was at least 30% higher than during the week after the cessation of menstruation. Each of the 11 patients also met the DSM-III-R criteria for late luteal phase dysphoric disorder. All of the subjects admitted to carbohydrate craving during the late luteal phase of the cycle. The women participated in two 5-hour GTTs: one during the late follicular phase (within the week following day 6 of the menstrual cycle) and one during the late luteal phase (during the last 6 days of the menstrual cycle). These women were

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asked to consume at least 150 g of carbohydrate per day for 3 days and were provided with an extensive list of good sources of carbohydrate and the estimated grams of carbohydrate per item on the list; the subjects were also instructed to fast overnight before the GTT.

All studies started between 8:00 a.m. and 10:00 a.m. An intravenous line for blood sampling was inserted at least 15 minutes before the sampling began. After a sample for measurement of fasting blood sugar was drawn, an oral glucose challenge (1.5 g/kg of body weight, up to 100 g) was administered. Blood samples for determination of plasma glucose levels were obtained at 30-minute intervals for 5 hours. The blood was immediately placed on ice, centrifuged, and sent for plasma glucose determination. At each 30-minute time point the patients completed the modified Spielberger State Anxiety Scale (15) and visual analogue scales for 27 variables, including anxiety, mood, palpitations, hunger, sweating, dizziness, and shakiness. In addition, each patient completed the Beck Depression Inventory (16) at baseline and at the 5-hour time point.

As suggested by other authors (17–19), a patient was considered to have chemical hypoglycemia if she had either a plasma glucose nadir below 60 mg/dl or a hypoglycemia index higher than 0.8 and a plasma glucose nadir less than 65 mg/dl (the hypoglycemia index is the fall in glucose during the 90 minutes before the nadir divided by the glucose nadir). For this study, we chose the more conservative measure, plasma glucose level, instead of blood glucose level (the plasma glucose level generally is approximately 10%–15% higher than the blood glucose value). Patients were considered to have clinically relevant symptoms if they spontaneously reported symptoms associated with hypoglycemia (such as shakiness, sweating, and palpitations) or if their self-ratings on the visual analogue scales indicated significantly more symptoms than at baseline for at least two of the following six variables: anxiety, palpitations, hunger, sweating, dizziness, and shakiness.

The Student's *t* test was used to compare the baseline scores on the mood self-rating tests during the follicular and luteal phases. To analyze the effect of time during the GTT on the mood self-ratings and on the glucose levels, analysis of variance (ANOVA) with repeated measures was used. A Fisher's exact test was performed to compare the prevalences of hypoglycemia during the different menstrual cycle phases. To determine whether the patients' ratings indicated significantly more symptoms during the glucose nadir, we performed Student's *t* tests to compare the mean score for the visual analogue scale self-ratings from baseline to 60 minutes before the nadir with the mean of the ratings done 30 minutes before to 30 minutes after the nadir. Where appropriate, multivariate test statistics (Wilks' lambda) were employed.

**TABLE 1. Hypoglycemia in 11 Women With PMS During Glucose Tolerance Testing in the Luteal and Follicular Phases of the Menstrual Cycle**

Hypoglycemia Measure	Number of Patients	
	Luteal Phase	Follicular Phase
Chemical hypoglycemia		
Plasma glucose nadir <60 mg/dl	7	5
Hypoglycemia index <sup>a</sup> >0.8 and plasma glucose nadir <65 mg/dl	6	5
Either criterion	8	6
Clinical symptoms of hypoglycemia <sup>b</sup>	8	7
With chemical hypoglycemia	7	5
Without chemical hypoglycemia	1	2

<sup>a</sup>Defined as fall in glucose level during 90 minutes before nadir divided by glucose level at nadir.

<sup>b</sup>Spontaneously reported symptoms associated with hypoglycemia or significant increase in self-ratings on visual analogue scales for anxiety, palpitations, hunger, sweating, dizziness, and shakiness.

## RESULTS

In the luteal phase, eight of the 11 patients were clinically symptomatic during the GTT, and in the follicular phase seven of the 11 patients were clinically symptomatic during the GTT (table 1). Eight of the 11 patients had chemical evidence of hypoglycemia in the luteal phase, while six met the criteria in the follicular phase. While many of the patients in the study experienced chemical hypoglycemia, there was no significant difference in the frequency of hypoglycemia between the follicular phase and the luteal phase (Fisher's exact test). In general, patients who met the criteria for chemical hypoglycemia in the follicular phase were the same ones who met them in the luteal phase. Of the 14 GTTs during which chemical hypoglycemia was observed, 12 were associated with clinical symptoms; of the eight GTTs without evidence of chemical hypoglycemia, three were associated with clinical symptoms ( $p < 0.05$ , Fisher's exact test).

The onset of hypoglycemia symptoms occurred at the time of the nadir or within 30 minutes after the nadir in all the patients who experienced such symptoms. All of these patients uniformly stated that the symptoms experienced during the GTT were dissimilar to their PMS symptoms. For example, irritability is common to both PMS and hypoglycemia, but during the GTT the visual analogue scale self-ratings for the angry/irritable item were significantly higher at the nadir compared with the baseline for only two of the 11 patients in the luteal phase and for only three patients during the follicular phase. Further, a paired *t* test comparison of the mean anger/irritability ratings at baseline and during the nadir revealed no significant increase in anger/irritability in either menstrual cycle phase (follicular phase:  $t = 1.25$ ,  $df = 10$ ,  $p > 0.05$ ; luteal phase:  $t = 1.98$ ,  $df = 10$ ,  $p > 0.05$ ). In addition, although sad mood is associated with PMS, only one patient had significantly higher self-ratings on the visual analogue

**TABLE 2. Glucose Levels in 11 Women With PMS During Glucose Tolerance Testing in the Luteal and Follicular Phases of the Menstrual Cycle**

Menstrual Cycle Phase	Glucose Level (mg/dl)						Time of Nadir (min)	
	Baseline <sup>a</sup>		Peak		Nadir		Mean	SD
	Mean	SD	Mean	SD	Mean	SD		
Luteal (symptomatic)	90.7	4.0	141.4	29.4	57.5	8.7	223.6	59.0
Follicular (asymptomatic)	91.0	6.7	141.3	37.6	59.5	9.1	223.6	52.6

<sup>a</sup>After carbohydrate loading and overnight fast.

scale item indicating sadness, and this occurred during the follicular phase.

No difference in glucose tolerance related to menstrual cycle phase was found by using an ANOVA with repeated measures ( $F=0.18$ ,  $df=1, 10$ , n.s.). In fact, the mean fasting, peak, and nadir glucose levels observed in the follicular and luteal phases were almost identical (table 2). The response to the GTT varied among the patients, but most patients had similar results in the two menstrual cycle phases.

A two-way ANOVA with repeated measures of the Beck Depression Inventory scores at baseline and at 5 hours revealed no significant effect for menstrual cycle phase ( $F=4.85$ ,  $df=1, 9$ ,  $p=0.06$ ) or time ( $F=1.27$ ,  $df=1, 9$ ,  $p=0.29$ ) and no significant Phase by Time interaction ( $F=4.11$ ,  $df=1, 9$ ,  $p=0.07$ ). The near effect for phase reflected sadder mood during the luteal phase (baseline score= $13.6\pm7.6$ ) than during the follicular phase ( $4.4\pm5.7$ ) (paired  $t=2.99$ ,  $df=9$ ,  $p<0.05$ ). An ANOVA with repeated measures for the Spielberger State Anxiety Scale scores (obtained every 30 minutes) indicated an effect for menstrual cycle phase (reflecting more anxiety during the luteal phase) ( $F=15.20$ ,  $df=1, 10$ ,  $p<0.01$ ), no effect for time during the GTT ( $F=28.49$ ,  $df=10, 1$ , n.s.), and no Phase by Time interaction ( $F=19.18$ ,  $df=10, 1$ , n.s.). The Spielberger State Anxiety Scale scores also reflected more symptoms at baseline during the luteal phase than during the follicular phase (luteal phase:  $49.4\pm11.7$ ; follicular phase:  $34.5\pm12.1$ ; paired  $t=3.76$ ,  $df=10$ ,  $p<0.05$ ). Some patients experienced symptoms of clinical hypoglycemia at their glucose nadirs but did not experience increased mood ratings (anxiety, anger, and depression).

We examined the effect of menstrual cycle phase on the total symptom score (the total for all 27 items rated with the visual analogue scales) obtained during the GTT. An ANOVA with repeated measures showed no significant Phase by Time interaction, indicating that any changes in the overall severity of symptoms seen during the GTT were not a function of menstrual cycle phase. We also examined the effect of menstrual cycle phase on the degree of increase in symptoms during the GTT. The increase was defined as the mean of the total symptom scores obtained from the baseline to 60 minutes before the glucose nadir subtracted from the mean of the total symptom scores obtained from 30 minutes before to 30 minutes after the nadir. For five subjects the greatest increase in total symptom score was dur-

ing the luteal phase, and for six subjects the greatest increase occurred during the follicular phase. The mean $\pm$ SD percentage of increase in self-ratings for all symptoms was  $174.5\%\pm229.2\%$  for the follicular phase and  $88.6\%\pm71.0\%$  for the luteal phase; the percentage of increase in the self-ratings for hypoglycemia symptoms (anxiety, palpitations, hunger, sweatiness, dizziness, and shakiness) was  $345.0\%\pm535.4\%$  for the follicular phase and  $244.8\%\pm167.8\%$  for the luteal phase.

## DISCUSSION

In this study, patients with prospectively confirmed PMS were given GTTs during the follicular and luteal phases of the menstrual cycle. The patients were in different mood states during the two phases, as demonstrated by significantly higher baseline scores on the Beck Depression Inventory and the Spielberger State Anxiety Scale during the luteal phase. Evidence of hypoglycemia during the GTT in these 11 women with PMS was obtained during both the luteal and follicular phases, on the basis of both chemical measures (eight and six subjects, respectively) and clinical measures (eight and seven subjects, respectively). These prevalences appear high when compared with those in normal samples (17, 20) but are comparable to the rate reported for another psychiatric sample by Uhde et al. (21). Of those nine patients with panic disorder, eight had plasma glucose nadirs below 60 mg/dl during GTTs. Our results are also comparable to those of Reid et al. (11), who reported that four of six PMS patients experienced clinical symptoms of hypoglycemia in both phases of the menstrual cycle. When our patients experienced chemical hypoglycemia, they typically also had clinical symptoms of hypoglycemia. Because we did not perform GTTs on normal control subjects, it is unclear whether the prevalences we observed are abnormally high. It is, nonetheless, clear that the hypoglycemia we observed was not specific to the luteal phase. Many patients rated themselves as suffering from typical symptoms of hypoglycemia, such as trembling ( $N=5$ ) or sweating ( $N=7$ ), whereas they generally did not rate themselves as having more irritability or depression, symptoms often endorsed by those suffering from PMS. Additionally, when asked if the symptoms during the GTT paralleled those constituting their PMS, the patients uniformly responded in



the negative. In the study by Uhde et al. (21), panic disorder patients reported that the symptoms experienced during the study were qualitatively different from their naturally occurring panic attacks. It therefore appears that differences in glucose tolerance related to menstrual cycle phase cannot be responsible for PMS. It further appears that while PMS symptoms overlap those experienced during hypoglycemia, they are sufficiently different to warrant abandoning the hypothesis that PMS is hypoglycemia.

## REFERENCES

1. Moss RH: Typology of menstrual cycle symptoms. *Gynecology* 1968; 103:390-402
2. Dalton K: *The Premenstrual Syndrome*. Springfield, Ill, Charles C Thomas, 1964
3. Rubinow DR, Roy-Byrne PP: Premenstrual syndromes: overview from a methodologic perspective. *Am J Psychiatry* 1984; 141:163-172
4. De Pirro R, Fusco A, Bertoli A, et al: Insulin receptors during the menstrual cycle in normal women. *J Clin Endocrinol Metab* 1978; 47:1387-1389
5. Jarrett RJ, Graver HJ: Changes in oral glucose tolerance during the menstrual cycle. *Br Med J* 1968; 2:528-529
6. Billig HE Jr, Spaulding CA Jr: Hyperinsulinism of menses. *Industrial Med* 1947; 16:336-339
7. Morton JH: Premenstrual tension. *Am J Obstet Gynecol* 1950; 60:343-352
8. Roy SK, Ghosh BP, Bhattacharjee SK: Changes in oral glucose tolerance during normal menstrual cycle. *J Indian Med Assoc* 1971; 57:201-204
9. Cudworth AG, Veevers A: Carbohydrate metabolism in the menstrual cycle. *Br J Obstet Gynecol* 1975; 82:162-169
10. Spellacy WN, Carlson KL, Schade SL: Menstrual cycle carbohydrate metabolism. *Am J Obstet Gynecol* 1967; 9:382-386
11. Reid RL, Greenaway-Coates A, Hahn PM: Oral glucose tolerance during the menstrual cycle in normal women and women with alleged premenstrual "hypoglycemic" attacks: effects of naloxone. *J Clin Endocrinol Metab* 1986; 62:1167-1171
12. Bonara E, Zavaroni I, Alpi O, et al: Influence of the menstrual cycle on glucose tolerance and insulin secretion. *Am J Obstet Gynecol* 1987; 157:140-141
13. Permutt MA, Delmez J, Stenson W: Effects of carbohydrate restriction on the hypoglycemic phase of the glucose tolerance test. *J Clin Endocrinol Metab* 1976; 43:1088-1093
14. Rubinow DR, Roy-Byrne PP, Hoban MC, et al: Prospective assessment of menstrually related mood disorders. *Am J Psychiatry* 1984; 141:684-686
15. Spielberger CB, Gorsuch RL, Lushene RE: *STAI Manual for the State-Trait Anxiety Inventory*. Palo Alto, Calif, Consulting Psychologists Press, 1970
16. Beck AT, Ward CH, Mendelson M, et al: An inventory for measuring depression. *Arch Gen Psychiatry* 1961; 4:561-571
17. Jung Y, Khurana RC, Corredor DG, et al: Reactive hypoglycemia in women. *Diabetes* 1971; 20:428-434
18. Fabrykant M: Clinical versus laboratory hypoglycemia: an analysis of 81 oral glucose tolerance tests with arterial and venous blood glucose measurements. *Metabolism* 1955; 4:153-159
19. Hadji-Georgopoulos A, Schmidt MI, Margolis S, et al: Elevated hypoglycemia index and late hyperinsulinism in symptomatic postprandial hypoglycemia. *J Clin Endocrinol Metab* 1980; 50:371-376
20. Lev-Ran A, Anderson RW: The diagnosis of postprandial hypoglycemia. *Diabetes* 1981; 30:996-999
21. Uhde TW, Vittone BJ, Post RM: Glucose tolerance testing in panic disorders. *Am J Psychiatry* 1984; 141:1461-1463

# Tridimensional Personality Questionnaire Scores of Sons of Alcoholic and Nonalcoholic Fathers

Marc A. Schuckit, M.D., Michael Irwin, M.D., and Heike I.M. Mahler, Ph.D.

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*The authors studied 33 men whose fathers had severe alcohol-related problems and 33 subjects with no family history of alcoholism. The former supplied information about the course of their fathers' alcohol problems; all 66 men answered questions about their own drinking and drug use and completed the Tridimensional Personality Questionnaire. There were no significant relationships between any of the 18 questionnaire scores and a subject's quantity/frequency of drinking or his family history of alcoholism. There was only one significant correlation between the alcoholic fathers' type 2 characteristics, according to the type 1/type 2 theory, and the sons' questionnaire scores. The relevance of these findings to the theory is discussed.*

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The causes of alcoholism, the treatment needs, and the clinical patterns among alcoholics appear to be diverse. Even after diagnostic criteria for alcoholism are carefully used to identify the 70% or more of alcoholic men and women with no prior psychiatric syndromes, the remaining patients probably still represent multiple subpopulations with unique characteristics.

One attempt to identify relevant patient subgroups has been made by Cloninger et al. (1, 2), who place alcoholics either into two extreme subtypes or on a continuum based on their clinical characteristics and personality profiles. They hypothesize that men and women with the type 1 extreme have a disorder that is more responsive to environment and less related to genetic factors, in which the onset of relatively mild alcohol problems occurs after the age of 25. According to this theory, type 1 alcoholics are eager to please, are sentimental, seek social approval (i.e., demonstrate high reward dependence), are cautious and likely to worry (i.e., have high harm avoidance), and tend to be

reserved and a bit rigid (i.e., show low novelty seeking) (2). The typical type 2 alcoholic is a man who has a disorder that is thought to be highly influenced by heredity, with early onset of severe and violence-related alcohol problems and a high propensity to abuse drugs. His personality has the characteristics of high novelty seeking along with low reward dependence and low harm avoidance (1-4 and unpublished paper by C.R. Cloninger et al., 1983). It is further hypothesized that novelty seeking is principally related to dopamine activity, harm avoidance to serotonin, and reward dependence to the norepinephrine neurochemical system (2).

As we have recently discussed in other articles (5, 6), this model can be difficult to test directly. Most studies have looked at more oblique validators, evaluating the outcome of logical predictions that should be true if the original premises were correct. For example, in three separate studies (3, 4, 7), von Knorring et al. used a related series of definitions of type 2 attributes to place alcoholics into two discrete categories on the basis of 1) the age at which the first major life problems due to alcohol use or the first alcoholism treatment occurred and 2) the incidence of social complications resulting from use of alcohol. In the first study (4), consistent with predictions, there was a higher prevalence of drug abuse and criminality among the type 2 men; however, inconsistent with predictions, these same individuals, when compared to type 1 men, did not demonstrate a greater risk of psychiatric disorders themselves and there was no greater rate of alcoholism in their fathers. In the second study (7), it was found that type 2 individuals were more aggressive and had more job problems related to alcohol use and more arrests, but the study was difficult to evaluate because some of the same social difficulties relating to job and arrests may have been involved in the definition of the type 2 individuals in the first place. In the third study (3), while type 2 men had an earlier onset of alcoholism and showed evidence of less socialization and higher levels of verbal aggression, contrary to expectations, there were no significant differences between type 1 and type 2 alcoholic men on measures of impulsiveness, indirect aggression, guilt, psychological anxiety, hostility, irritability, avoidance of monotony, or social desirability when they were tested with the Karolinska Scales of Personality.

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Received April 25, 1989; revision received Aug. 22, 1989; accepted Sept. 14, 1989. From the School of Medicine, University of California, San Diego, and the Alcohol Research Center, San Diego VA Medical Center. Address reprint requests to Dr. Schuckit, Department of Psychiatry, VA Medical Center, 3350 La Jolla Village Dr., San Diego, CA 92161.

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Cloninger et al. also have evaluated some individual components of their theory. For example, after transposing teachers' ratings of 233 11-year-old boys into analogues of the three personality dimensions addressed on the Tridimensional Personality Questionnaire, they found that reward dependence had little power, whereas high novelty seeking and/or low harm avoidance were able to predict the 30 individuals who were considered to have abused alcohol by age 27 (1). Also consistent with their hypothesis, in a separate study male relatives of female alcoholics were different from male relatives of male alcoholics on several characteristics—a finding consistent with the hypothesized higher prevalence of type 1 alcoholism among women (1, 2).

Several recent studies from our own laboratory have also attempted to test indirectly the relevance of the concept of type 1 and type 2 alcoholism. In the first evaluation (5), the predictions inherent in the theory were explored in 31 sons of carefully defined primary alcoholic fathers. The fathers' alcoholism was rated on a scale of 0–5 using characteristics typical of the type 2 extreme, including onset of severe alcohol problems before the age of 25, multiple arrests for drunk driving, multiple arrests for public intoxication or drunk and disorderly conduct, a history of treatment for alcoholism, and the absence of any female alcoholic first-degree relatives. If a predisposition to type 2 alcoholism is genetically transmitted, then the study could have revealed that the sons of men with more type 2 characteristics were more likely than the sons of type 1 men to show an early onset of drinking, greater alcohol and drug intake, and associated problems. However, the evaluations did not show any of these predictions to be accurate with respect to the sons' patterns of drug and alcohol intake.

A second investigation from our group (6) evaluated characteristics of a separate sample of actual alcoholics and also produced negative findings. The study examined whether the clinical course of primary alcoholics was associated with age at onset of alcohol-related problems and with the type 1/type 2 classification scheme. In that study, interviews with 171 primary alcoholic men consecutively entering an alcohol treatment program revealed that age at onset of alcoholism was by itself correlated with histories of alcohol, drug, and childhood criminality problems. Once the age at onset of alcoholism was considered, neither classifying these alcoholics into discrete type 1 and type 2 categories nor placing them along a continuum of type 2 characteristics as defined by their life pattern of problems was consistently associated with the severity of the clinical alcoholic histories. These findings underscore the clinical importance of age at onset of alcoholism and suggest the possibility that the type 2 prototype represents a separate diagnosis—antisocial personality disorder—and not alcoholism itself.

The present investigation further expanded our efforts to test the type 1/type 2 hierarchy as presently proposed. To complement the two studies we have just

outlined, in this protocol we undertook an analysis of the three major personality characteristics evaluated on the Tridimensional Personality Questionnaire in a sample of 66 men: 33 sons of alcoholic fathers and 33 control subjects. We hypothesized 1) that regardless of family history, the young men who engaged in heavier drinking would be more likely to demonstrate the type 2 profile on the questionnaire, with higher levels of novelty seeking and lower levels of harm avoidance and reward dependence; 2) that the sons of alcoholics would be more likely to demonstrate type 2 characteristics than the sons of nonalcoholics; and 3) that type 2 characteristics would be especially likely to be observed in the heaviest drinkers among the sons of alcoholics.

## METHOD

The 66 men included in this study were identified and tested through two stages of work (8, 9). As described previously (5, 6, 8, 9), first a structured questionnaire was sent to all male students and nonacademic staff members at the University of California, San Diego, who were 18–25 years old. They were asked to supply demographic information and describe their medical and smoking histories, their drinking and drug-use patterns and problems, and the alcohol-related life problems of any of their first-degree relatives. The definitions of psychiatric illness and substance abuse disorders for the subjects and for their first-degree relatives followed those outlined in *DSM-III*. Potential subjects were excluded from the study if they had serious medical or psychiatric disorders or met the *DSM-III* criteria for alcohol or substance abuse disorder (all exclusions added up to approximately 10% of the potential subjects, including less than 2% who were excluded for alcohol abuse or dependence).

Selected individuals were then telephoned to corroborate key historical data, after which they were invited to the laboratory for further evaluations that included part of an interview (10) and drawing of blood samples. The latter were used to exclude persons who were likely to have been drinking heavily enough to alter body functioning, as demonstrated by elevated values for  $\gamma$ -glutamyltransferase level, mean corpuscular volume, liver function tests, uric acid level, etc. (11, 12).

Subsequently, over the next 3 years, 33 young men whose fathers met the *DMS-III* criteria and the Research Diagnostic Criteria (RDC) (13) for alcoholism (alcohol abuse or dependence) in the absence of any major preexisting psychiatric disorder were chosen for the group with positive family histories of alcoholism (14). Eight of these individuals had been included in a prior study (5). Because of the presence of alcoholism in a first-degree relative, these men would be expected to have approximately a fourfold greater risk of alcoholism themselves during their lifetimes (8, 9). For each of these higher-risk men, a family-history-negative control subject was selected on the basis of the



**TABLE 1. Alcohol-Related Factors Reported for Fathers of 33 Men With Positive Family Histories of Alcoholism**

Factor	N	%
Alcohol problem before age 25	7	21
Multiple arrests for drunk driving	7	21
Multiple arrests for being drunk and disorderly or for public intoxication	5	15
Lack of a female alcoholic first-degree relative	32	97
Treatment for alcoholism or experience with Alcoholics Anonymous	20	61

lack of any psychiatric disorder, including alcoholism or drug abuse, in any first- or second-degree relative. The individuals with positive and negative family histories were similar in age, sex, race, religion, educational level, quantity and frequency of alcohol intake, and drug use history.

As in a prior study (5), the father of each individual with a family history of alcoholism was assigned a score of 0 to 5 on the basis of the number of type 2 alcohol-related factors reported for the father. These five alcohol-related factors were chosen for evaluation because of their relevance to the theory of Cloninger and his associates (15) as well as their ready availability in the database already gathered for each individual. The five factors for the father included a first major life problem resulting from use of alcohol before the age of 25, multiple (two or more) arrests for drunk driving, multiple arrests for public intoxication or drunk and disorderly conduct, a history of prior treatment for alcoholism or experience with Alcoholics Anonymous, and lack of a female alcoholic first-degree relative (see table 1). The analyses relevant to the fathers' scores were, of course, carried out only for the group who had family histories of alcoholism.

As part of the protocol, all 66 men were asked to fill out the Tridimensional Personality Questionnaire (1, 2). The fourth version of this questionnaire, circulated in May 1987, consists of 100 true/false questions and takes approximately 10–15 minutes to fill out. Following the guidelines presented by Cloninger et al. (1, 2), we divided the scoring system into three major dimensions: novelty seeking (nine subscales, including three that are generated from the combination of the results of other subscales, and a total score), harm avoidance (four subscales and a total score), and reward dependence (two subscales and a total score). While these are listed in the official scoring key as 18 separate scores, the impulsive (versus reflective) and the impulsiveness versus reflection scores are generated from the same items.

The potential relevance of the Tridimensional Personality Questionnaire scores of these 66 young men (33 pairs of family-history-positive and family-history-negative subjects) was tested through a series of steps. The initial analyses evaluated in detail the relationship between personality profiles and drinking histories or family history status. These results were further explored in order to better understand the potential in-

teraction between the drinking and family factors as they relate to personality profiles. First, to test the prediction that regardless of family history, the heavier-drinking individuals among the 66 men would be more likely to demonstrate higher levels of novelty seeking and lower levels of harm avoidance and reward dependence, we performed a median split based on the quantity times the frequency of alcohol intake in the preceding 3 months. The 32 individuals whose results were above the split and who demonstrated a higher quantity/frequency and the 34 who had a lower quantity/frequency were then compared on all total scores and subtests of the Tridimensional Personality Questionnaire. We used Student's *t* test to compare the two groups.

In the second analysis, based on the assumption that the subjects with family histories of alcoholism might have a genetic predisposition toward alcoholism, the Tridimensional Personality Questionnaire scores of the 33 sons of alcoholics were compared to the scores of the 33 sons of nonalcoholics, again by means of Student's *t* test. Third, to look at interactions, we performed a two-way analysis of variance (ANOVA) evaluating the impact of quantity and frequency (high or low intake of ethanol) and the impact of family history of alcoholism (positive or negative). Finally, after we assigned each alcoholic father a score of 0–5 on the basis of the father's characteristics on the type 1/type 2 continuum, that score and the son's scores on the Tridimensional Personality Questionnaire were evaluated with Pearson's correlation coefficient.

## RESULTS

Consistent with the samples tested in our laboratory over the years (5, 6, 8, 9), the 66 subjects had an average age of about 22 years, approximately 15 years of education, and religious preferences equally divided among Protestant, Catholic, and no affiliation. The alcohol consumption histories revealed that, on average, the first drink was taken at 14 years. The usual consumption of alcoholic beverages over the preceding 3 months consisted of drinking on about 8 days per month, with an intake of about three drinks per occasion (a drink was defined as 12 oz of beer, 4 oz of wine, or 1.5 oz of an 80-proof beverage). While many men had had an isolated alcohol-related difficulty such as a blackout or forgetting part of what happened during an evening of drinking, none had severe-enough problems to be considered as having alcohol abuse or dependence. Almost 90% (*N*=57) of the sample had at some time used a drug, most frequently marijuana, and a smaller percentage had had experience with other drugs of abuse. On the basis of the matching procedures, there were no significant differences on any of these variables when the individuals with family histories of alcoholism were compared with those without such a history.

In the first major analysis, presented in table 2, the

**TABLE 2. Mean Subscale Scores on the Tridimensional Personality Questionnaire of 66 Men Divided Into Groups First by Quantity/Frequency of Drinking and Then by Family History of Alcoholism**

Subscale	Quantity/Frequency of Drinking					Family History of Alcoholism				
	Higher (N=34)		Lower (N=32)		t (df=64)	Positive (N=33)		Negative (N=33)		t (df=64)
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Novelty seeking	17.0	4.73	17.8	4.72	0.68	17.4	4.05	17.4	5.35	0.03
Exploratory (versus rigid)	4.3	1.31	4.4	1.16	0.13	4.5	0.91	4.2	1.47	1.01
Disorderly (versus regimented)	2.7	1.42	2.8	1.39	0.22	2.5	1.35	3.0	1.42	-1.24
Excitable/fickle (versus stoic/loyal)	2.3	1.03	2.8	1.05	1.77	2.7	0.98	2.4	1.11	1.41
Impulsive (versus reflective)	2.8	2.08	2.6	1.81	-0.40	2.3	1.88	3.0	1.94	-1.61
Dramatic/talkative (versus laconic/listener)	2.4	1.38	2.2	1.28	-0.43	2.4	1.39	2.2	1.28	0.37
Extravagant (versus frugal)	2.5	1.91	3.1	1.39	1.75	3.0	1.37	2.6	1.25	1.31
Exploratory excitability versus stoic rigidity	6.7	1.89	7.1	1.76	1.09	7.2	1.28	6.6	2.22	1.49
Impulsiveness versus reflection	2.8	2.08	2.6	1.81	-0.40	2.3	1.88	3.0	1.94	-1.61
Extravagance versus reserve	7.6	2.28	8.1	3.07	0.74	7.9	2.63	7.8	2.83	0.18
Harm avoidance	8.8	5.18	9.5	5.62	0.47	9.2	5.64	9.1	5.19	0.11
Anticipatory worry and pessimism (versus uninhibited optimism)	1.3	1.52	1.5	1.56	0.49	1.6	1.52	1.3	1.55	0.88
Tension about uncertainty or physical danger	2.4	2.12	2.9	2.09	1.03	2.6	2.03	2.7	2.21	-0.17
Shyness with strangers	3.0	2.13	2.7	1.93	-0.71	2.8	2.34	2.9	1.82	0.36
Fatigability and asthenia	2.1	1.05	2.3	1.25	0.92	2.2	1.17	2.2	1.15	0.32
Reward dependence	19.8	4.77	21.2	4.40	1.29	21.2	4.50	19.8	4.68	1.21
Social sensitivity versus detachment	12.1	3.82	13.6	3.61	1.67	13.5	3.55	12.2	3.91	1.38
Persistence	7.7	2.32	7.6	2.27	-0.13	7.7	2.25	7.6	2.33	0.16

median split was used to divide the 66 men, regardless of family history, into a group with lower and a group with higher quantity/frequency of alcohol intake over the preceding 3 months. The two groups had means  $\pm$  SD of  $5.6 \pm 3.46$  and  $11.2 \pm 5.62$  days per month, respectively, on which drinking occurred ( $t = -4.81$ ,  $df = 50.92$ ,  $p < 0.001$ ). They had consumed  $2.5 \pm 1.16$  and  $4.02 \pm 1.26$  drinks, respectively, per average occasion ( $t = -4.93$ ,  $df = 64$ ,  $p < 0.001$ ). The mean  $\pm$  SD quantity times frequency of alcohol intake was  $14.4 \pm 10.69$  versus  $41.5 \pm 16.87$  ( $t = -7.75$ ,  $df = 51.88$ ,  $p < 0.001$ ). (Note that the degrees of freedom were based on a separate variance figure because of possible inequality of variance for the groups.) If Tridimensional Personality Questionnaire scale scores indicate individuals who are more likely to have engaged in heavy drinking early in life, then one would predict significantly higher scores on the novelty seeking subscales for the heavier drinkers, while that same group would be likely to have lower scores on harm avoidance and reward dependence. The first three columns of table 2 indicate that no such differences occurred. According to the three total scores, the heavier-drinking group had an unexpected *lower* score on novelty seeking, although they did demonstrate a trend toward lower scores on harm avoidance and reward dependence. A power analysis using the approach of Cohen (16) showed that to obtain a power of 0.8 with a difference between

groups significant at  $p < 0.05$  for each of the three total scores, samples of 1090, 972, and 308 men, respectively, would have been required.

The second group of three columns in table 2 shows the Tridimensional Personality Questionnaire scores of the 66 men divided into two groups according to the presence or absence of a family history of alcoholism ( $N = 33$  in each group). We predicted that the former would demonstrate higher levels of novelty seeking along with lower levels of harm avoidance and reward dependence. However, there were no significant differences between the two family history groups on any of the 18 test scores, nor were there consistent trends in the predicted directions. The only difference among the three total scores was a *higher* score on reward dependence for the men with alcoholic fathers, a finding that would reach statistical significance if 298 pairs had been studied (16).

Another analysis was done in which the 33 men with family histories of alcoholism were studied separately. They were divided on a median split of higher and lower quantity/frequency of alcohol intake. Once again, there were no significant differences on any Tridimensional Personality Questionnaire scale score, including no difference between the heavier and lighter drinkers in mean  $\pm$  SD total novelty seeking score ( $17.9 \pm 4.02$  and  $17.0 \pm 4.15$ , respectively;  $t = -0.61$ ,  $df = 31$ ,  $p = 0.54$ ), total score for harm avoidance ( $9.2 \pm 5.49$

and  $9.3 \pm 5.94$ , respectively;  $t=0.05$ ,  $df=31$ ,  $p=0.96$ ), and total reward dependence score ( $21.1 \pm 4.67$  and  $21.4 \pm 4.47$ ;  $t=0.18$ ,  $df=31$ ,  $p=0.86$ ). From these results, one would correctly predict that when a series of  $2 \times 2$  ANOVAs was carried out for each of the 18 Tridimensional Personality Questionnaire scores in relation to the effects of family history of alcoholism, quantity/frequency of alcohol intake, and the interaction between the two, no significant main effects or interactions would be observed across any of the scores.

It might be argued that using a median split to divide the men into groups with higher and lower quantity/frequency of alcohol intake, although appropriate, resulted in some moderate drinkers being included in each group, which might have masked any true differences in questionnaire scores between the higher and lower quantity/frequency groups. Thus, as a further step in evaluating the potential relationship between quantity/frequency of drinking and scores on the Tridimensional Personality Questionnaire, the 25% of the subjects who were the heaviest drinkers were compared to the 25% who had the lowest alcohol intake. The mean  $\pm$  SD values for drinking over the preceding 3 months for the two groups included  $14.2 \pm 6.35$  and  $3.3 \pm 1.92$  days of drinking per month, respectively ( $t=-6.56$ ,  $df=17.73$ ,  $p<0.001$ ),  $3.4 \pm 0.81$  and  $2.1 \pm 1.20$  drinks per occasion, respectively ( $t=-3.45$ ,  $df=30$ ,  $p=0.002$ ), and a quantity times frequency of  $47.1 \pm 18.90$  versus  $7.7 \pm 7.01$  ( $t=-7.83$ ,  $df=19.05$ ,  $p<0.001$ ). Once again, no significant differences on questionnaire scores across groups were noted.

The final analysis of this series is presented in table 3. Here, the 33 alcoholic fathers were characterized on a type 1/type 2 continuum on the basis of the presence or absence of the five characteristics described in the Method section. None of the fathers had zero type 2 characteristics, 18% ( $N=6$ ) of the fathers had one type 2 characteristic, 61% ( $N=20$ ) had two such characteristics, 15% ( $N=5$ ) had three, none had four, and 6% ( $N=2$ ) had five. One would expect the number of type 2 characteristics displayed by an alcoholic father to be positively correlated with his son's score on the novelty seeking subscale of the Tridimensional Personality Questionnaire and negatively correlated with his son's scores on the harm avoidance and reward dependence subscales. The sons' questionnaire scores were compared with the fathers' scores on a 0- to 5-point scale. Table 3 demonstrates that of the 18 potential scores generated by the Tridimensional Personality Questionnaire, only one, the sons' score on the extravagant versus frugal subscale of novelty seeking, was significantly correlated in the expected direction with the fathers' type 2 characteristics, and even this correlation was relatively modest. With respect to the three total subscale scores, power analyses (16) showed that if 193 men had been studied, correlations for both the novelty seeking and harm avoidance scores would have been significant, but the latter would have been in the opposite direction to that predicted by Cloninger

**TABLE 3. Correlations Between 33 Men's Tridimensional Personality Questionnaire Subscale Scores and Their Fathers' Alcohol-Related Problem Scores**

Subscale	r (df=31)	p
Novelty seeking	0.25	0.15
Exploratory (versus rigid)	0.16	0.37
Disorderly (versus regimented)	-0.09	0.61
Excitable/fickle (versus stoic/loyal)	-0.02	0.90
Impulsive (versus reflective)	0.22	0.21
Dramatic/talkative (versus laconic/listener)	0.05	0.77
Extravagant (versus frugal)	0.39	0.03
Exploratory excitability versus stoic rigidity	0.10	0.58
Impulsiveness versus reflection	0.22	0.21
Extravagance versus reserve	0.18	0.31
Harm avoidance	0.19	0.30
Anticipatory worry and pessimism (versus uninhibited optimism)	0.08	0.63
Tension about uncertainty or physical danger	0.26	0.15
Shyness with strangers	0.18	0.31
Fatigability and asthenia	-0.01	0.97
Reward dependence	0.13	0.48
Social sensitivity versus detachment	0.25	0.16
Persistence	-0.14	0.43

and associates. To double-check our results, we compared the questionnaire scores of the men whose fathers scored in the highest and lowest quartiles on the 0-5 scale. Consistent with the correlation findings reported for the entire sample of subjects with alcoholic fathers,  $t$  tests revealed no significant group differences in the predicted directions.

## DISCUSSION

A search is now underway to identify important subgroups among alcoholics. The successful characterization of alcoholic subsamples may help highlight individuals with unique clinical conditions and/or treatment needs. Establishing relevant subtypes is also an important initial step in any successful attempt to further our understanding of genetic markers of alcoholism, because the more homogeneous the population under study, the greater the chance of relevant results.

In this light, Cloninger and colleagues have performed a great service to our field. They have proposed a theory that highlights the heterogeneity among alcoholics, the potential impact of both genetic and environmental factors, and the possibility that different influences might be relevant in different alcoholic subgroups. They have also produced a relatively detailed theory that can be considered, at least partially tested, and modified.

The present study is the third of a series of investigations by our group attempting to test indirectly the validity of the type 1/type 2 theory by evaluating pre-



dictions made from the theoretical construct. In this study we assumed that higher levels of novelty seeking and lower levels of harm avoidance and reward dependence would be observed among the young men who were the heaviest drinkers as well as among those who had alcoholic fathers. On the basis of the type 1/type 2 theory, it was further predicted that the simultaneous consideration of both family history and quantity/frequency of drinking among young adult men would help identify those with the greatest loading for type 2 characteristics, and that these two factors might be related in an even more impressive way to the three hypothesized personality dimensions than either the pattern of intake or the family history alone. Finally, it was assumed that the more clinical characteristics consistent with type 2 alcoholism that a father demonstrated, the greater the likelihood that his son would show a type 2 profile on the Tridimensional Personality Questionnaire.

None of the predictions was supported by the data. These results are consistent with the two other evaluations carried out by our group. First, a prior analysis (5) demonstrated that the clinical characteristics of the sons' drinking and drug use histories did not correlate in any predicted way with the fathers' positions on a type 1/type 2 continuum that used factors similar to those we have described. Second, in an evaluation of a totally separate group (6)—a consecutive series of alcoholics entering an alcohol treatment program—the individual alcoholic's score on a type 1/type 2 continuum based on his clinical characteristics did not correlate with additional characteristics that would have been predicted from the theory. Indeed, the level of relationship between the alcoholic's clinical course and factors that might have been predicted by the theory was explained almost totally by one item, the subject's age at onset of the first major life problem resulting from alcohol use. This factor, early onset of severe alcohol-related problems, is not new as a correlate of the clinical course; it has been discussed in the literature since at least the 1960s (17, 18). The ability of a single item to explain most of the relationship with the clinical course in that earlier study raises questions about the need for the more sophisticated full theory proposed by Cloninger and colleagues. The results of the present analyses are also consistent with many of the findings of von Knorring et al. (3, 4, 7), who noted many inconsistencies between the type 1/type 2 continuum and personality characteristics among alcoholics.

As we have stated before (5, 6), it is important to recognize that findings inconsistent with a theory in no way disprove the overall hypothesis. On the other hand, a definitive test of the type 1/type 2 theoretical model in which clinical course, personality characteristics, and possible neurochemical mediators are considered is difficult to carry out. As a result, many of the evaluations done by Cloninger and colleagues, by von Knorring and associates, and by our group only indirectly test the hypothesis by evaluating predictions that one would expect to be valid on the basis of the hy-

pothetical construct. Until a definitive test of the overall theory can be devised, clinicians and theoreticians will have to rely on indirect evaluations such as those we have reported.

It is also important to remember that the deficiencies in any indirect measure of a hypothesis become even more glaring when the findings are basically negative (5, 6). In this light, there were imperfections inherent in the present study. For example, no Tridimensional Personality Questionnaire scores were available for the fathers; the alcoholic fathers' characteristics on a type 1/type 2 continuum were generated from the best information reported by their sons and in a telephone interview with a relative whenever the available information was incomplete. In addition, the subjects for the study were selected from among young adult employees and students at a university, which raises the possibility that potential subjects in their late teens or early twenties who had extreme type 2 characteristics were excluded from the study because such persons are unable to hold jobs or perform as students and thus were unavailable.

On the other hand, the sample (N=66) is large enough to begin to test these questions. Indeed, our power analyses indicated that for the differences between groups on all six total subscale scores in table 2 to have been significant, an average of about 800 subjects would have been required, and even then some of the results would have been the opposite of those predicted by Cloninger and associates. Another strength of the study is that projections inherent in the type 1/type 2 continuum were tested through a variety of mechanisms, including establishing the relationship between heavier drinking and Tridimensional Personality Questionnaire scores among the subjects, the relationship between family history and questionnaire scores among the subjects, the interaction between family history and heavier drinking as they relate to personality measures, and the relationship between the fathers' characteristics and their sons' scores on the questionnaire. Considering the 18 potential scores on the questionnaire and the multiple dimensions on which the questionnaire data were analyzed, we would have expected more than one significant result among the more than 50 analyses we carried out.

We feel that it is likely that the prototype type 2 alcoholic actually has a separate disorder, antisocial personality disorder. Compared to alcoholics, men with antisocial personality disorder have a markedly different premorbid course and unique levels of resistance to treatment, and they may evidence separate genetic influences (5, 6, 18–22). Thus, despite the high prevalence of alcohol and drug problems secondary to antisocial personality disorder, it is no more logical to consider men with this disorder to be alcoholics than it would be to give an individual who is depressed during cocaine withdrawal a diagnosis of an independent affective disorder. Our negative results may reflect the relative absence of antisocial personality disorder in our subjects and their fathers.

In conclusion, consistent with other studies reported from our laboratory, the data from the current study do not support the potential clinical relevance of the Tridimensional Personality Questionnaire in identifying subjects with unique characteristics related to their drinking histories, family histories, or characteristics of their fathers' alcoholism. At the very least, this may indicate that the theory of Cloninger and associates does not apply equally well to all potential subgroups. At the most, the results might indicate that the overall theoretical construct requires important revisions.

## REFERENCES

1. Cloninger CR, Sigvardsson S, Bohman M: Childhood personality predicts alcohol abuse in young adults. *Alcoholism (NY)* 1988; 12:494-505
2. Cloninger CR: Neurogenetic adaptive mechanisms in alcoholism. *Science* 1987; 236:410-416
3. von Knorring L, von Knorring AL, Smigan L, et al: Personality traits in subtypes of alcoholics. *J Stud Alcohol* 1987; 48:523-527
4. von Knorring L, Palm U, Andersson H: Relationship between treatment outcome and subtype of alcoholism in men. *J Stud Alcohol* 1985; 46:388-391
5. Schuckit M, Irwin M: An analysis of the clinical relevance of type 1 and type 2 alcoholics. *Br J Addict* 1989; 84:869-876
6. Irwin M, Schuckit M, Smith TL: Clinical importance of age at onset in type 1 and type 2 primary alcoholics. *Arch Gen Psychiatry* (in press)
7. von Knorring AL, Bohman M, von Knorring L, et al: Platelet MAO activity as a biological marker in subgroups of alcoholism. *Acta Psychiatr Scand* 1985; 72:51-58
8. Schuckit MA: Biological vulnerability to alcoholism. *J Consult Clin Psychol* 1987; 55:301-309
9. Schuckit MA: Reactions to alcohol in sons of alcoholics and controls. *Alcoholism (NY)* 1988; 12:465-470
10. Schuckit MA, Irwin M, Howard TL, et al: A structured diagnostic interview for identification of primary alcoholism: a preliminary evaluation. *J Stud Alcohol* 1987; 49:93-99
11. Irwin M, Baird S, Smith TL, et al: Use of laboratory tests to monitor heavy drinking by alcoholic men discharged from a treatment program. *Am J Psychiatry* 1988; 145:595-599
12. Schuckit MA, Irwin M: Diagnosis of alcoholism. *Med Clin North Am* 1988; 72:1133-1153
13. Spitzer RL, Endicott J, Robins E: Research Diagnostic Criteria: rationale and reliability. *Arch Gen Psychiatry* 1978; 35:773-782
14. Schuckit MA: The clinical implications of primary diagnostic groups among alcoholics. *Arch Gen Psychiatry* 1988; 42:1043-1049
15. Gilligan SB, Reich T, Cloninger CR: Alcohol-related symptoms in heterogeneous families of hospitalized alcoholics. *Alcoholism (NY)* 1988; 12:671-678
16. Cohen J: *Statistical Power Analysis for the Behavioral Sciences*. New York, Academic Press, 1969
17. Schuckit MA, Gunderson EK: Alcoholism in young men. *Am J Drug Alcohol Abuse* 1977; 4:581-592
18. Foulds GA, Hassall C: The significance of age of onset of excessive drinking in male alcoholics. *Br J Psychiatry* 1969; 115:1027-1032
19. Cloninger CR, Gottesman II: Genetic and environmental factors in antisocial behavior disorders, in *The Cause of Crime: New Biological Approaches*. Edited by Mednick SA, Moffitt TE, Stack SA. New York, Cambridge University Press, 1987
20. Cadoret RJ: Psychopathology in adopted-away offspring of biologic parents with antisocial behavior. *Arch Gen Psychiatry* 1978; 35:176-184
21. Cadoret RJ, O'Gorman TW, Troughton E, et al: Alcoholism and antisocial personality: interrelationships, genetic and environmental factors. *Arch Gen Psychiatry* 1985; 42:161-167
22. Cadoret RJ, Troughton E, O'Gorman TW: Genetic and environmental factors in alcohol abuse and antisocial personality. *J Stud Alcohol* 1987; 48:1-8

## Paradoxical Patient Reactions to Psychiatric Life Support: Clinical and Ethical Considerations

Samuel L. Pauker, M.D., and Arnold M. Cooper, M.D.

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*The authors describe cases illustrating two types of high-risk and especially difficult suicidal psychiatric inpatients. In the first case, a suicidal patient reacted to psychiatric life support measures (maximum observation) with increasingly life-threatening acting out, necessitating a difficult, seemingly paradoxical staff decision to withdraw life support. In the second, a patient felt to be improving killed herself when life support was withdrawn. The authors argue that there are clinical limits to psychiatric life support and an appropriate goal of psychiatric treatment is to maximize the chances for patient survival, rather than to attempt to guarantee such survival.*

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The two clinical situations we present in this article are not new to clinicians; indeed, they are all too familiar. These two clinical challenges consume much inpatient staff time and energy in the form of deliberation and concern. In one case, this deliberation was prospective: How should we proceed with a suicidal patient who reacted negatively to our efforts to keep her alive? The other involved a retrospective evaluation of what was done for a suicidal patient who seemed to be improving but then precipitously committed suicide.

We present these cases because we feel there is an important clinical reality that tends to be overlooked and/or denied and may be unintegrated in the thinking of clinicians and of society at large. It is that there is a limit to the powers of our current clinical art and sci-

ence to keep psychiatric patients alive and sometimes our efforts to foster patient improvement entail taking potentially life-threatening risks. Taking such risks is inherent in good care, given the limits of our current therapeutic capacity.

Few clinical situations are as difficult and frightening to psychiatrists as the care of the seriously suicidal patient who fails to respond to treatment. Some patients remain overtly suicidal despite great efforts to provide treatment and life support. In fact, at times our attempts to guarantee survival by the use of life support systems—such as constant observation—may exacerbate psychopathology or deprive the patient of an opportunity to achieve a reasonable level of autonomy.

By “psychiatric life support” we mean procedures that keep psychiatric patients alive but are not directed at ameliorating psychopathology. While medical life support usually entails complex modern technologies, psychiatric life support involves one-to-one monitoring of suicidal patients and the interventions required to restrain patients from harming themselves, such as physical restraint or sedation. Psychopharmacology, psychotherapy, and other psychosocial interventions are also used in this effort and are usually aimed at modifying the course of a disorder, in contrast to life support, which is intended to keep a patient alive until the course of illness is modified. There are patients, however, whose underlying disorders are refractory to the treatment interventions currently known to us. We may observe these patients for long periods of time, get to know them as well as we can, and apply successive therapeutic regimens as intensively as possible, and the patient may still remain suicidal (1–4).

The cases of two patients follow. For the first, extended life support seemed to inhibit recovery. In the second, additional life support might have prevented a suicide.

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## CASE REPORTS

*Case 1: The Treatment-Refractory Suicidal Patient*

Ms. A, an unmarried 29-year-old woman, had been given diagnoses of dysthymic disorder and mixed personality disorder. This was her fifth psychiatric hospitalization for depression and suicidality, which had followed the breakup of her relationship with a boyfriend. Ms. A's hospital care included multiple drug treatments for her depression (including phenelzine, lithium, L-triiodothyronine, trazodone, lorazepam, alprazolam, and various combinations of these agents) and intensive psychotherapy, with little improvement. She required 3½ months of almost continuous observation because of her increasingly life-threatening acting out. Multiple consultations were sought regarding both drug treatment and her milieu treatment with maximum observation. A senior consultant felt that the maximum observation had become countertherapeutic, causing Ms. A to regress in the hospital, and that the somatic and psychotherapeutic modalities were providing her little benefit, as she continued to be actively suicidal.

Since the life support was felt to be harming rather than helping, it was decided to gradually reduce the observation. Ms. A and her family were carefully apprised of the reasons for this course of action and the significant risks involved. As this treatment plan proceeded, Ms. A was observed to be "re-organizing" herself, functioning in a less dependent manner, and exhibiting less sadomasochistic acting out. During this period she superficially cut her wrists and hinted at a plan to hang herself, but the staff felt that these were more attention-seeking gestures than truly suicidal endeavors. Mobilization proceeded and Ms. A was eventually able to be discharged to an outpatient therapist with whom she had a close working alliance.

This case illustrates that our usual hospital treatment modalities may exacerbate rather than ameliorate a patient's condition, creating an environment that induces clinical regression and the potential for further life-threatening behavior. The multiple expert consultations requested reflect the extreme danger that the staff perceived for this patient. Ultimately the staff recognized that their best treatment efforts had been ineffective and that providing a risk-free environment was antitherapeutic. They then attempted to fashion a treatment that might help to promote the patient's well-being by enhancing her autonomy and responsibility, rather than providing total protection from risk. The treatment team also appreciated that the risks of this decision must be shared with the patient and her family.

As the staff's adoption of Ms. A's ego functions was cautiously reversed and monitoring was withdrawn, she made a series of suicidal gestures that, fortunately but not predictably, were of minimal seriousness. The treatment strategy was successful in this instance. Ms. A had a good therapeutic alliance with an outpatient psychiatric psychotherapist, which helped sustain her during this process, and she was eventually able to be discharged. We emphasize, however, that the patient might have killed herself, and that other patients in sim-

ilar circumstances have done so and will do so in the future.

In the following case vignette, the patient appeared to be doing better than Ms. A but killed herself when life support was tapered.

*Case 2: The Suicidal Patient Who Seems to be Improving*

Ms. B, a young unmarried woman, had been admitted for psychiatric hospitalization because of acute psychosis and suicidal ideation. Her adolescence had been marked by multiple symptoms, including sexual promiscuity, religiosity, rebellion against her parents, substance abuse (marijuana and some cocaine), and bulimia. She had also exhibited bizarre behaviors, such as stating that she could communicate with tiny creatures, having odd decorations in her room, and treating pet animals sadistically. Ms. B's one prior psychiatric hospitalization had been related to her eating disorder; she believed her "stomach was connected to the center of the earth." Before her current hospitalization she had been paranoid and said she was being manipulated by the television and radio. The bizarre nature and chronicity of her symptoms and a prior poor response to lithium led to the diagnosis of schizophrenia.

After her workup, Ms. B was treated with neuroleptics, psychotherapy, and various milieu therapeutic modalities. Given the protracted nature of her illness, after due consideration the staff believed that Ms. B's best chance for both survival and achievement of the maximum level of adaptation of which she was capable would be best served by long-term hospitalization.

Ms. B's initial hospital course was unremarkable. Although she was psychotic (i.e., had ideas of reference, thought others were speaking her thoughts, and exhibited paranoia) and suicidal, Ms. B was able to come to the staff when feeling suicidal, was reassured by their attention, and responded well to restriction to the unit's central lounge.

On hospital day 13, Ms. B came in contact with an elderly depressed male patient, which seemed to upset her greatly. Afterward she precipitously and surreptitiously eloped with a strong intent to obtain razor blades and to swallow them and kill herself. She was found and brought back to the hospital by her mother. After her return, she continued to be psychotic and suicidal. Her neuroleptic dose was increased. The elopement was felt by the staff to signal a significant change; Ms. B could no longer be counted on to come to the staff for help when feeling acutely suicidal. From day 13 on, therefore, she was placed on round-the-clock observation.

With the increased neuroleptic dose, Ms. B's paranoid ideation diminished. Her active suicidal ideation persisted, however, and the maximum observation was continued. ECT was considered but postponed in the belief that it might interfere with efforts to facilitate Ms. B's transfer for long-term care. Indeed, with the higher dose of neuroleptic her mood began to brighten. She rejoined activities and was much less suicidal.

After 22 days of round-the-clock observation her status was downgraded, and her monitoring was decreased to checks every 15 minutes during the day and constant observation at night. For 12 days, at this level of monitoring, Ms. B was able to participate in some activities and was more communicative with the staff, in whom she could now confide her periodic passive suicidal ideation.

On hospital day 47, after 34 days of total or partial observation, it was felt that maximum observation could be discontinued. Three days later Ms. B continued to appear to be doing well. After a pleasant telephone call with her mother and a conversation with a staff nurse, neither of whom detected any special difficulty, with no evident precipitant Ms. B went into a bathroom stall, put a plastic bag over her head, and asphyxiated herself. She was found a short time later and was given cardiopulmonary resuscitation but was eventually found to be brain dead.

A follow-up mortality and morbidity conference was held, as is the hospital's usual procedure after a death. It was uniformly thought that Ms. B's diagnosis and treatment had been appropriate. Her diagnosis (schizophrenia) and demoralization were seen as high-risk factors in the case. However, Ms. B had seemed to be doing better at the time of her suicide and during the days before it, after maximum observation had been withdrawn.

This case highlights a number of clinical and ethical points. Despite our best clinical efforts we cannot always predict underlying suicidality, especially in our schizophrenic patients (5, 6). When a patient is improving, as Ms. B was, and we are trying to switch the patient to less restrictive long-term treatment, we attempt to transfer self-care functions back to the patient.

Cases such as this one make us wonder if extending monitoring for suicidality beyond the point of apparent clinical improvement would prevent many suicides. Despite the potential merits of such an option, clinicians would generally find this an ill-advised and unacceptable clinical precaution. Unlike the monitoring of patients who have had myocardial infarctions, who may experience life-threatening arrhythmias, psychiatric life support may be an invasive procedure associated with morbidity itself and may delay the patient's reacquisition of self-care capabilities or, as in the first case, stimulate regressive self-destructive acts.

## DISCUSSION

We have identified two kinds of suicidal patients who are difficult to manage. The first type seems to worsen with maximum observation and improve when it is terminated and the patient is given increased responsibility for his or her own care. The second type seems to be improving but is at risk for unexpected suicide when maximum observation is withdrawn. Currently there are no means of identifying either type of patient despite careful clinical attention. Careful study and research are needed to diminish the time required to identify the first type of patient and to devise some form of extended observation or monitoring for the second. Despite our best efforts, however, we are faced with and will continue to be faced with a central clinical ethical dilemma. Psychiatric recovery entails the patient's eventually regaining responsibility

for his or her own care. Since this is an important part of the recovery process, some small percentage of patients will at some point present the kind of risk described in case 2.

The question of when life support may ethically be discontinued has preoccupied medicine since technology has been able to sustain physiological functioning in patients who are no longer sentient or whose hopelessness and suffering—and their wish for relief from the pain of life—would lead to a wished-for death in the absence of life support (7). The comparable response in psychiatry is not technologic; rather, it invokes a social procedure—maximum observation—to maintain life in a patient whose psychiatric disorder leads to the determination to die and who does not respond to available treatments. A psychiatric hospital has an obligation to 1) provide a safe haven for the patient, 2) carefully consider all diagnostic possibilities, 3) offer all appropriate treatments, 4) work assiduously at understanding the patient and family to help them overcome any resistance to compliance, 5) alert the patient and family to the risks and limitations, as well as benefits, of any treatment effort, 6) take steps to protect the patient with all available life support measures pending successful treatment, and 7) recognize when a treatment has failed or is contributing further to morbidity.

As psychiatrists, we may find it difficult to accept that a small percentage of our suicidal patients are refractory to the currently available interventions and that acceptance of this risk is a critical part of the care of psychiatric patients. Like their counterparts in oncology and other medical and surgical subspecialties that deal with the severely and terminally ill, some of these patients, despite our best efforts, will die. Our task is to maximize life support for those who will benefit from our treatments while, with the greatest caution, we attempt to identify that small group who cannot benefit from and may be harmed by prolonged psychiatric life support procedures. At some point in the care of the nonpsychotic, chronically suicidal patient, we must examine whether life support measures are contributing to the patient's morbidity and whether their usefulness justifies the drain on the resources available for the care of other patients.

Paradoxically, some patients appear to do worse with maximum observation and respond well to the judicious return of self-care functions (as in case 1), while some who seem to be improving surprise us with impulsive lethal acts (as in case 2). Clearly, both groups deserve additional study and research. Until we better understand the nature of the impulsive, "unpredictable" suicide and since we cannot and should not keep all improving patients under extended maximum observation, we must accept that facilitating patient improvement and autonomy will engender a small but significant unavoidable risk of mortality.

REFERENCES

1. Robins LN, Kulbok PA: Methodological strategies in suicide, in Psychobiology of Suicidal Behavior. Edited by Mann JJ, Stanley M. New York, Annals of the New York Academy of Sciences, 1986
2. Linehan MM: Suicidal people: one population or two? Ibid
3. Cohen J: Statistical approaches to suicidal risk factor analysis. Ibid
4. Pfeffer CR: Suicide prevention: current efficacy and future promise. Ibid
5. Johns CA, Stanley M, Stanley B: Suicide in schizophrenia. Ibid
6. Salama AA: Depression and suicide in schizophrenic patients. Suicide Life Threat Behav 1988; 18:379-384
7. Rachels J: Barney Clark's key. Hastings Cent Rep 1983; 13(2): 17-19



## **Trial of Fluoxetine Added to Neuroleptics for Treatment-Resistant Schizophrenic Patients**

**Donald C. Goff, M.D., Andrew W. Brotman, M.D., Meredith Waites, R.N.,  
and Scott McCormick, M.D.**

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*Mean ratings of positive and negative symptoms and depression significantly improved in nine treatment-resistant schizophrenic patients who completed a 6-week open trial of fluoxetine added to their neuroleptics. The authors identify differences between responders and nonresponders and recommend controlled trials.*  
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**A**lthough conventional antipsychotics produce substantial improvement in the majority of schizophrenic patients, effective treatments for nonresponders or partial responders are not currently available. One approach to supplementing dopaminergic blockade in the treatment of schizophrenia has been the use of serotonergic agents. Preliminary trials with serotonergic agents have shown positive, although inconsistent, effects in combination with antipsychotics.

Both serotonergic agonists and serotonergic antagonists have been reported to improve schizophrenic symptoms—a circumstance that is difficult to interpret but that may reflect the complexity of multiple serotonin (5-HT) receptor types. The immediate precursor of 5-HT, 5-hydroxytryptophan, is reported to block amphetamine-induced worsening of psychotic symptoms in schizophrenic patients (1). In preliminary studies, fenfluramine, which decreases plasma levels of 5-HT, has been associated with mixed clinical effects. In a recent double-blind trial, fenfluramine significantly

worsened psychopathology in eight schizophrenic patients (2). Among direct serotonin antagonists, both the nonselective agent cyproheptadine and the selective 5-HT<sub>2</sub> antagonist ritanserin have been associated with therapeutic effects (3, 4). These preliminary trials indicate that serotonergic agents may have therapeutic activity in some schizophrenic patients; however, it is currently not possible to predict what effect an agonist or antagonist may produce.

We report here a pilot study in which the selective 5-HT reuptake blocker fluoxetine (5) was added to the neuroleptic treatment of chronic, symptomatic schizophrenic patients. Our rationale for undertaking this open trial was initially based on the theory that negative symptoms might benefit from a serotonergic agonist. To our knowledge, the use of fluoxetine in treating schizophrenia has not yet been reported.

### **METHOD**

The subjects were adult outpatients with diagnoses of schizophrenia or schizoaffective disorder, according to *DSM-III-R* criteria, who were treated at a university-affiliated community mental health center. Patients were referred by their clinicians on the basis of their having chronic, clinically significant positive or negative symptoms despite good compliance with their treatment regimens for at least 1 year before the study began. Their medication regimens had remained unchanged for at least 6 months before they entered the study. In addition to neuroleptics, anticholinergic agents and benzodiazepines were the only concurrent medications; these were continued unchanged during the study.

After giving informed consent to participate, patients were assessed at baseline with the Brief Psychiatric Rating Scale (BPRS), the Hamilton Rating Scale

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TABLE 1. Symptom Scores of Nine Schizophrenic Patients Who Completed a 6-Week Trial of Fluoxetine Added to Their Neuroleptics

Scale	Baseline		Week 2		Week 4		Week 6	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
BPRS <sup>a</sup>	46.6	11.1	34.1	5.6	31.6	5.6	31.4	2.6
Negative symptom scale <sup>b</sup>	48.3	11.8	35.9	13.7	44.6	13.6	37.3	13.0
Hamilton depression scale <sup>c</sup>	15.3	11.2	13.3	12.8	10.9	12.2	9.1	9.3
GAS <sup>d</sup>	33.0	3.5	37.7	10.0	41.8	5.8	38.1	7.9

<sup>a</sup>Significant difference ( $p < 0.05$ ) between baseline and week 2 ( $t = 3.19$ ,  $df = 8$ ), week 4 ( $t = 3.29$ ,  $df = 7$ ), and week 6 ( $t = 3.23$ ,  $df = 8$ ).

<sup>b</sup>Significant difference ( $p < 0.05$ ) between baseline and week 2 ( $t = 2.33$ ,  $df = 8$ ) and week 6 ( $t = 2.67$ ,  $df = 8$ ).

<sup>c</sup>Significant difference ( $p < 0.05$ ) between baseline and week 4 ( $t = 4.38$ ,  $df = 7$ ) and week 6 ( $t = 3.05$ ,  $df = 7$ ).

<sup>d</sup>Significant difference ( $p < 0.05$ ) between baseline and week 4 ( $t = 4.12$ ,  $df = 7$ ).

for Depression, the Scale for Assessment of Negative Symptoms, and the Global Assessment Scale (GAS). *DSM-III-R* diagnoses were established by direct clinical interviews plus chart review and were confirmed by a consensus diagnostic conference with each patient's primary clinician. Patients with current major depression or past intolerance of antidepressants were excluded.

Fluoxetine was administered orally at a daily dose of 20 mg to all patients during a 6-week trial. The scales administered at baseline were given to each subject again at weeks 2, 4, and 6 by a single nonblind rater. In addition, at week 6 the patient's primary clinician was asked to rate the patient's global response as much improved, moderately improved, unchanged, or worse.

Mean scores on each of the rating scales at baseline and at weeks 2, 4, and 6 were compared using paired-sample, two-tailed  $t$  tests.

## RESULTS

Fourteen patients (13 with schizophrenia and one with schizoaffective disorder, depressed type) started the study, and nine patients completed the 6-week trial. Five patients dropped out within the first 3 days of the fluoxetine trial: two complained of agitation and feeling overstimulated, two complained of drowsiness and fatigue, and one complained of epigastric discomfort. Dropouts did not differ from completers in mean age, neuroleptic dosage, or score on any of the baseline rating scales.

The eight men and one woman who completed the 6-week trial had a mean  $\pm$  SD age of  $38.3 \pm 12.8$  years. Their mean  $\pm$  SD daily neuroleptic dose was  $900 \pm 447$  mg of chlorpromazine equivalents, and their mean  $\pm$  SD duration of illness was  $15.6 \pm 10.4$  years.

As shown in table 1, at week 6 mean scores were significantly lower than at baseline on the BPRS (33%), the Hamilton scale (40%), and the negative symptom scale (23%). The GAS score was significantly improved (27%) at week 4 only. Scores on individual items on the BPRS were reduced from baseline to week 6 as follows: suspiciousness, 51%; hallucinatory behavior, 30%; conceptual disorganization, 32%; and unusual thought content, 15%. Four of the nine patients were rated by their primary clinicians at week 6 as moderately or much improved, five as unchanged,

and none as worse. The four patients who were identified by their clinicians as responders were younger than the nonresponders ( $28.5 \pm 8.8$  versus  $46.2 \pm 9.7$  years) and had a shorter duration of illness ( $9.2 \pm 5.4$  versus  $20.6 \pm 11.1$  years). The responders also had a higher mean  $\pm$  SD baseline BPRS score ( $51.6 \pm 10.3$  versus  $38.3 \pm 13.3$ ) and baseline Hamilton depression score ( $20.6 \pm 12.6$  versus  $8.8 \pm 4.0$ ). None of these differences was statistically significant.

## DISCUSSION

The finding that fluoxetine appeared to significantly improve both positive and negative psychotic symptoms, as well as depressive symptoms, in treatment-resistant schizophrenic patients can only be considered as preliminary pending replication by double-blind trials. Undoubtedly, fluoxetine benefited from a halo effect, owing to the enthusiasm associated with using a new medication. However, we did not expect to find an effect on positive symptoms, and the study patients had previously failed to improve in multiple trials of adjuvant medication.

If fluoxetine improves symptoms in a subgroup of schizophrenic patients, the mechanism is unclear. The fact that responders had substantial ratings of depression at baseline suggests that the benefit we found may in part reflect a nonspecific antidepressant effect. However, none of the patients met criteria for major depression, and nondepressive symptoms such as auditory hallucinations and delusions were equally responsive. Siris et al. (6) added imipramine to neuroleptics for schizophrenic patients with major and minor depression and found a significant therapeutic response, but this improvement was restricted to signs of depression.

Another possible explanation for our findings is a pharmacokinetic interaction between fluoxetine and neuroleptics. Fluoxetine is reported to increase blood levels of tricyclic antidepressants (7), and such an effect on neuroleptics might have been anticipated on the basis of a report that extrapyramidal symptoms worsened with the addition of fluoxetine to neuroleptic treatment (8). An increase in blood levels of neuroleptics seems an unlikely explanation for the therapeutic effect in this study, however, since most of the patients

were already receiving moderately high doses and had taken higher doses in the past without benefit. We did not observe worsening of extrapyramidal symptoms in the present trial, although formal examination for neurological side effects was not done.

Another possible mechanism for the therapeutic effect observed in this open trial is a specific effect of 5-HT on schizophrenic symptoms. This could reflect a defect in 5-HT regulation in some neuroleptic-resistant schizophrenic patients. Studies of CSF and plasma levels of 5-HT and 5-hydroxyindoleacetic acid, as well as preliminary neuroendocrine challenge tests, have suggested that a subgroup of schizophrenic patients may have abnormalities in serotonergic regulation (9). Fluoxetine increases brain levels of 5-HT through specific inhibition of reuptake. The effect of repeated dosing with fluoxetine on 5-HT receptors remains less clear, as most studies have found no effect; however, one study reported evidence for down-regulation of high-affinity 5-HT receptor sites (5). Alternatively, fluoxetine may act indirectly in these patients by regulating dopaminergic activity. Serotonergic pathways exhibit complex interactions with dopaminergic systems, including the inhibitory regulation of activity of forebrain dopamine-containing areas (10).

Double-blind trials are necessary to further evaluate the therapeutic benefit and adverse effects of fluoxetine as an adjuvant to neuroleptics in treatment-resistant schizophrenic patients. Given the present lack of effective treatment options for these patients and the recent

advances in our understanding of the complex actions associated with agents acting on multiple serotonergic receptor types, further work with fluoxetine and related compounds is of potential importance.

## REFERENCES

1. Irwin MR, Marder SR, Fuentenebro F, et al: L-5-Hydroxytryptophan attenuates positive psychotic symptoms induced by D-amphetamine. *Psychiatry Res* 1987; 22:283-289
2. Marshall BD Jr, Glynn SM, Midha KK, et al: Adverse effects of fenfluramine in treatment refractory schizophrenia. *J Clin Psychopharmacol* 1989; 9:110-115
3. Silver H, Blacker M, Weller MP, et al: Treatment of chronic schizophrenia with cyproheptadine. *Biol Psychiatry* 1989; 25:502-504
4. Gelders Y, Vanden Bussche G, Reyntjens A, et al: Serotonin-52 receptor blockers in the treatment of chronic schizophrenia. *Clin Neuropharmacol* 1986; 9:325-327
5. Sommi RW, Crismon ML, Bowden CL: Fluoxetine: a serotonin-specific, second-generation antidepressant. *Pharmacotherapy* 1987; 7:1-15
6. Siris SG, Adan F, Cohen M, et al: Targeted treatment of depression-like symptoms in schizophrenia. *Psychopharmacol Bull* 1987; 23:85-89
7. Vaughan DA: Interaction of fluoxetine with tricyclic antidepressants (letter). *Am J Psychiatry* 1988; 145:1478
8. Tate JL: Extrapyramidal symptoms in a patient taking haloperidol and fluoxetine (letter). *Am J Psychiatry* 1989; 146:399-400
9. Bleich A, Brown S-L, Kahn R, et al: The role of serotonin in schizophrenia. *Schizophr Bull* 1988; 14:297-315
10. Jenner P, Sheehy M, Marsden CD: Noradrenaline and 5-hydroxytryptamine modulation of brain dopamine function: implications for the treatment of Parkinson's disease. *Br J Clin Pharmacol* 1983; 15(suppl):277s-289s



# Effect of Imipramine on Depression and Immune Status in a Sample of Men With HIV Infection

Judith G. Rabkin, Ph.D., M.P.H., and Wilma M. Harrison, M.D.

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*Eleven men with major depression and human immunodeficiency virus (HIV) infection underwent an open trial of imipramine. Eight of nine (89%) who completed 12 weeks responded. The mean decline in T4 cells from baseline was 100 at week 12 and 16 at week 26. No major exacerbations of HIV infection occurred.*

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Although depressive disorder among human immunodeficiency virus (HIV) seropositive men has been reported, we are unaware of any research regarding the efficacy of antidepressant treatment or its effect on the immune status of seropositive men who do not have a diagnosis of acquired immune deficiency syndrome (AIDS). Published findings of the impact of depression on immunocompetence have been inconsistent (1). For example, Kronfol et al. (2) reported a significantly diminished response to mitogen stimulation in 26 depressed patients compared to matched normal control subjects, but no significant effect of severity of depression within the patient group. In contrast, Schleifer et al. (3) found no overall difference in immune status between 91 depressed patients and matched normal control subjects. Severity of depression was associated with reduced mitogen proliferation but not with T cell count or natural killer cell activity. Earlier, Schleifer et al. (4) had reported reduced lymphocyte stimulation response in depressed hospitalized patients but not depressed outpatients. Maes et al. (5) found no differences in any immune parameter, including T4 cell count, associated with severity of depression among depressed inpatients. Overall, the relation between mood and immunocompetence requires further study.

The in vivo effect of antidepressants on immuno-

competence is largely unknown. Two small treatment studies have been reported in which no changes in immune status were found after treatment in patients with intact immune systems (6, 7). Miller et al. (8) analyzed the in vitro effects of tricyclics on natural killer cell activity. Desipramine had an inhibiting effect, while imipramine did not, at doses resembling those used in clinical practice. This work raises the possibility that there is further compromise of immune status by some tricyclic antidepressants in the context of HIV infection, although natural killer cell activity does not translate directly into clinical susceptibility, and the effect was not observed with imipramine.

In order to develop pilot data on these issues, we conducted an open study of imipramine in the treatment of homosexual men with major depressive disorder and HIV infection.

## METHOD

The sample consisted of 11 seropositive homosexual men and one seronegative homosexual man, who was included for purposes of confidentiality. To be included in the study, patients had to know their HIV test results beforehand, had to have major depressive disorder and no history of intravenous drug use, and had to give written, informed consent for their participation.

The patients' mean age was 43 years (range=31 to 56). Two patients had no history of any psychiatric disorder, seven had had past episodes of depression, one reported past alcohol abuse, and one had had both alcohol abuse and depression in the past. The course of their depressive illness was episodic rather than chronic, and current symptoms were predominantly endogenous (e.g., terminal insomnia) rather than atypical (e.g., oversleeping). The patients' medical status at baseline ranged from asymptomatic, with or without knowledge of low T4 cell count (N=5), to currently having HIV symptoms such as night sweats (N=3, including one patient taking azidothymidine). Three subjects had had past symptoms suggesting immune impairment, such as shingles and recurrent pulmonary infections, but were asymptomatic when they entered the study. There was no gross cognitive impairment, as assessed by the Mini-Mental State examination.

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Received July 6, 1989; revision received Sept. 12, 1989; accepted Oct. 31, 1989. From the New York State Psychiatric Institute and the Department of Psychiatry, College of Physicians and Surgeons, Columbia University, New York. Address reprint requests to Dr. Rabkin, New York State Psychiatric Institute, Box 35, 722 West 168th St., New York, NY 10032.

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The patients were treated on a fixed-dose schedule beginning with 25 mg/day of imipramine and increasing to 200 mg/day by day 14. After that, doses were increased as clinically indicated. Hamilton Rating Scale for Depression and Clinical Global Impression (CGI) ratings were made at baseline and at the end of 6 and 12 weeks. T cell subsets were assessed at baseline and at weeks 6, 12, and 26.

We present the absolute number of T4 cells per cubic millimeter of blood as our index of immune status and change. T4 cell count is qualitatively similar to other markers such as percentage of T4 cells or ratio of T4 to T8 cells (9) and has the advantages of simpler communication and broader recognition.

## RESULTS

After 6 weeks of treatment with imipramine at a mean $\pm$ SD dose of 225 $\pm$ 40 mg/day, the mean $\pm$ SD Hamilton depression score declined from 16.1 $\pm$ 3.5 to 6.4 $\pm$ 6.3. On the basis of achievement of a CGI score of 1 or 2 (much improved or very much improved) at week 6, seven patients were responders, one was a partial responder, and three were nonresponders. Between weeks 6 and 8, the drug was discontinued for two patients (because of a severe rash, which resolved after discontinuation, for one and because of continuing diarrhea, which led to low plasma levels of tricyclic antidepressant, for the other). At week 12, eight of the remaining nine patients were considered clear-cut responders, and one was still nonresponsive to imipramine, to which 25 mg/day of *d*-amphetamine had been added. This patient was then switched to fluoxetine, which was effective. Observed side effects for all patients were within the range of those seen in depressed patients without impaired immune status.

For the 11 patients who completed 6 weeks of treatment, the mean $\pm$ SD T4 cell count declined from 298 $\pm$ 125 to 279 $\pm$ 163, which was not statistically significant ( $t=0.29$ ,  $df=10$ , paired  $t$  test). For the nine patients who completed 12 weeks of treatment, the mean decline in T4 cell count (from a mean $\pm$ SD of 347 $\pm$ 69 to a mean of 247 $\pm$ 78) was statistically significant ( $t=2.86$ ,  $df=8$ ,  $p<0.001$ ). For the eight patients who completed 26 weeks of medication treatment (including the patient who was switched to fluoxetine after week 12), the mean decline in T4 cell count from baseline to week 26 was 16 cells, which was not statistically significant.

Table 1 shows the changes in T4 cell counts for the eight patients for whom we have complete data. The pattern of change parallels that reported for all patients at each occasion and shows that the transient drop and subsequent rise in T4 cell count seen cross-sectionally cannot be attributed to the departure from the sample of the patient included at week 12 and not included at week 26. Overall, the immune status measures reflect fluctuations during the 6-month period of observation, with substantial return to base-

TABLE 1. Changes in T4 Cell Count in Eight Depressed Men With HIV Infection Who Completed 6 Months of Treatment With Imipramine

Time	T4 Cell Count		Mean Change From Baseline	$t$ (df=7)	$p$
	Mean	SD			
Baseline	356	85	—	—	—
Week 6	307	134	-49	1.24	0.13
Week 12	246	84	-110	2.87	0.01
Week 26	340	163	-16	0.42	0.34

line levels and no clinical evidence of increased immune impairment.

## DISCUSSION

These preliminary results suggest that depressive disorder in the context of HIV infection is responsive to antidepressant medication. Many will find this surprising, given the real-life "depressogenic" situation; certainly, the patients were surprised and gratified. Furthermore, the effects of medication on T4 cell counts, while observable in the form of fluctuation in laboratory values, were apparently transient and not accompanied by increased infection. The 6-month mean decline of 16 T4 cells is actually less than expected with the passage of time; in HIV infection, there is an estimated annual decline of 100 T4 cells or 50 cells in 6 months (10).

In a longitudinal analysis of T cell counts in a community sample of homosexual men with HIV infection, Gorman (personal communication, 1989) found that five subjects with current major depression, who were not treated with antidepressants, had an average decline of 32 T4 cells over a 6-month interval. This is similar to the change we observed. These findings are preliminary evidence of the safety and efficacy of imipramine. We are undertaking a placebo-controlled imipramine study to confirm and extend these findings.

## REFERENCES

1. Calabrese JR, Kling MA, Gold PW: Alterations in immunocompetence during stress, bereavement, and depression: focus on neuroendocrine regulation. *Am J Psychiatry* 1987; 144:1123-1134
2. Kronfol Z, Silva J, Greden J, et al: Impaired lymphocyte function in depressive illness. *Life Sci* 1983; 33:241-247
3. Schleifer S, Keller S, Bond R, et al: Major depressive disorder and immunity. *Arch Gen Psychiatry* 1989; 46:81-87
4. Schleifer S, Keller S, Siris S, et al: Depression and immunity: lymphocyte function in ambulatory depressed patients, hospitalized schizophrenic patients, and patients hospitalized for herniorrhaphy. *Arch Gen Psychiatry* 1985; 42:129-133
5. Maes M, Bosmans E, Suy E, et al: Immune cell parameters in severely depressed patients: negative findings. *J Affective Disord* 1989; 17:121-128
6. Udelman D, Udelman H: A preliminary report on antidepressant therapy and its effects on hope and immunity. *Soc Sci Med* 1985; 20:1069-1072
7. Albrecht J, Helderma JH, Schlessner MA, et al: A controlled

- study of cellular immune function in affective disorders before and during somatic therapy. *Psychiatry Res* 1985; 15:185–193
8. Miller AH, Asnis GM, Van Praag HM: Tricyclic antidepressants and natural killer cell activity, in CME Syllabus and Proceedings Summary, 140th Annual Meeting of the American Psychiatric Association. Washington, DC, APA, 1987
  9. Taylor J, Fahey J, Detels R, et al: CD4 percentage, CD4 number, and CD4:CD8 ratio in HIV infection: which to choose and how to use. *J Acquired Immune Deficiency Syndromes* 1989; 2:114–124
  10. Munoz A, Carey V, Saah A, et al: Predictors of decline in CD4 lymphocytes in a cohort of homosexual men infected with human immunodeficiency virus. *J Acquired Immune Deficiency Syndromes* 1988; 1:396–404



# Reliability of Categorical and Dimensional Judgments of Personality Disorder

Kurt A. Heumann, B.A., and Leslie C. Morey, Ph.D.

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*To investigate interrater reliability on categorical and dimensional judgments of personality disorder, five clinicians completed five different judgment tasks for each of 10 case vignettes. The reliability estimates support previously unconfirmed statements that dimensional judgments are substantially more reliable than categorical diagnoses.*

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In recent years the classification of personality disorders has become a controversial topic. One important point of dissension surfacing in the literature is the appropriateness of a categorical model for pathological personality (1, 2). *DSM-III-R* and its precursor, *DSM-III*, provide categorical models for personality disorder that have not achieved high levels of interrater reliability. A number of authors have suggested that low reliability is an inevitable shortcoming of such models of personality disorder and that a dimensional model would be used with greater reliability. However, no empirical evidence directly supports this conclusion.

The purpose of the current study was to examine the reliability of different types of personality disorder judgments (i.e., categorical and dimensional) to determine which is more reliable. The focus of the study was on borderline personality disorder, which is the most prevalent personality disorder (3) and receives the largest proportion of research attention (4).

## METHOD

The participants in the study were five clinicians from the Nashville area who had a mean $\pm$ SD of 11.0 $\pm$ 7.5 years of clinical experience. Three were psychologists and two were psychiatrists. Each clinician was provided with a packet containing 10 case vignettes and information pertaining to making five different clinical judgments. The vignettes (available from

the second author on request) consisted of 10 prose case histories that were selected from various textbooks and monographs dealing with personality disorders. These 10 cases had been identified, through pilot testing, as representing a wide range of symptoms that are potentially relevant to the borderline personality construct.

The packet also included descriptive material and instructions for making the five judgments: 1) whether the patient fulfilled the *DSM-III-R* criteria for borderline personality disorder (i.e., a categorical judgment); 2) a dimensional prototypicality rating with regard to the borderline personality construct, with a high score reflecting a "prototypic" (5) borderline patient and a low score indicating that the patient was not similar to borderline patients; 3) a rating on Cloninger's (6) novelty seeking personality dimension, the description of which was taken verbatim from his original article; 4) a rating on Cloninger's reward dependent personality dimension, also taken verbatim from that article; and 5) a rating on the dominance-submission dimension of the Interpersonal Circumplex, taken verbatim from Leary (7). All four dimensional ratings were on 7-point scales. The clinicians were asked to read each case and then perform the five different diagnostic tasks. The order of the diagnostic decisions was counterbalanced across case histories, and the order of the case histories was randomized across subjects.

## RESULTS

Descriptive statistics for the ratings are provided in table 1. The reasonably large standard deviations of ratings across cases indicate that the cases represented a wide range of clinical material, further evidenced by the finding that the full 7-point range of ratings used was for each of the four dimensional measures.

A repeated measures analysis of variance (ANOVA) with each of the clinicians as the independent repeated variable, as described by Shrout and Fleiss (8), was calculated for each judgment task. The results were examined under two differing assumptions: 1) clinician as a fixed effect and 2) clinician as a random effect. From the ANOVA results, intraclass correlation coefficients (ICCs) were calculated in these two ways: the consistency of the clinician's ratings as measured

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Received May 15, 1989; revision received Sept. 28, 1989; accepted Nov. 1, 1989. From the Department of Psychology, Vanderbilt University. Address reprint requests to Dr. Morey, Department of Psychology, 301 A&S Psychology Bldg., Vanderbilt University, Nashville, TN 37240.

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**TABLE 1. Descriptive Statistics and Interrater Reliability Estimates for Five Clinicians Given Categorical and Dimensional Judgment Tasks Relating to Borderline Personality Disorder**

Judgment	Rating	Intraclass Correlation Coefficient <sup>a</sup>		Interrater Correlation	
		ICC-3	ICC-2	Mean	SD
Percent of cases diagnosed as borderline (categorical judgment)	22.0	0.1975 <sup>b</sup>	0.0796 <sup>b</sup>	0.1709	0.294
Prototypicality dimension <sup>c</sup>		0.5981 <sup>d</sup>	0.2703 <sup>d</sup>	0.6294	0.226
Mean	3.36				
SD	2.11				
Dominant/submissive dimension <sup>c</sup>		0.6086 <sup>d</sup>	0.6288 <sup>d</sup>	0.6382	0.256
Mean	3.63				
SD	2.30				
Novelty seeking dimension <sup>c</sup>		0.6788 <sup>d</sup>	0.3489 <sup>d</sup>	0.7052	0.308
Mean	4.29				
SD	1.93				
Reward dependent dimension <sup>c</sup>		0.4076 <sup>d</sup>	0.2817 <sup>d</sup>	0.4721	0.549
Mean	3.96				
SD	2.32				

<sup>a</sup>Formulas for intraclass correlation coefficients were taken from Shrout and Fleiss (8).

<sup>b</sup> $p < 0.05$ .

<sup>c</sup>7-point scale.

<sup>d</sup> $p < 0.001$ .

by ICC-3, with clinician as a fixed effect, and the level of agreement between clinicians as measured by ICC-2, with clinician as a random effect. ICC-3 is equivalent to coefficient alpha on the dimensional ratings and to KR-20 on the dichotomous categorical judgment; because coefficient alpha is an extension of KR-20, the two metrics allow a direct comparison of the relative reliability of the dichotomous and dimensional judgments.

The reliability values for the different judgments are presented in table 1. The ANOVA results indicated that all ICCs represented agreement significantly greater than chance. In all cases, the four dimensional judgments yielded reliability estimates greater than that of the categorical diagnosis.

Interrater correlation matrices were also calculated for each of the judgment tasks. The correlation coefficients were transformed using Fisher's  $z$  transformation, and these were averaged across all possible pairs of clinicians on each of the judgment tasks. These averages were then transformed back into correlation coefficients, and these are shown in table 1. To test whether the differences in interrater correlations were significant, paired-comparison  $t$  tests on all possible pairs of judgment tasks were calculated. Results indicated significant differences between borderline and prototypicality judgments ( $t=4.15$ ,  $df=9$ ,  $p<0.01$ ), borderline and dominant/submissive judgments ( $t=3.40$ ,  $df=9$ ,  $p<0.01$ ), borderline and novelty seeking judgments ( $t=3.89$ ,  $df=9$ ,  $p<0.01$ ), and novelty seeking and reward dependent judgments ( $t=2.43$ ,  $df=9$ ,  $p<0.05$ ).

## DISCUSSION

The results obtained in this study support the often cited contention that dimensional ratings of personal-

ity disorder are more reliable than categorical ones. Table 1 demonstrates that all three estimates of reliability are better for the dimensional ratings, and the results of the paired comparisons suggest that these differences are significant except in the case of the reward dependent scale.

While these data are encouraging, certain shortcomings should be kept in mind. The participants came from a variety of clinical settings but were from a limited geographical area. The use of written case vignettes, although widely done in previous reliability studies, imposes certain diagnostic limitations that may not pertain to live interviews. Furthermore, since the only categorical judgment task in the study involved borderline personality disorder, these results may not apply to other axis II or to axis I diagnoses. However, there is little reason to suspect that the results should be specific to the construct of borderline personality.

A valid construct loses clinical utility if diagnosticians cannot agree on it or are inconsistent in their ratings when using it. The results of this study suggest that this may be true for borderline personality disorder. While Mellsop et al. (9) found reliability of the borderline diagnosis to be somewhat higher ( $\kappa=0.29$ ), the reliability estimate from the current study, which may be used to generalize to other populations, was 0.0796. It was anticipated that including the *DSM-III-R* criteria verbatim in the material would lead to greater agreement. Thus, the low reliability of the categorical judgment found in this study is particularly noteworthy.

While these data do not point to any specific dimensional system as optimal, they do provide empirical support for the claim that dimensional systems of personality disorder are more reliable than categorical systems. However, these results do not imply that a

dimensional model is necessarily a more *valid* representation of personality disorder than a categorical approach. Determining the dimensions that best map the domain of personality disorders is a different question, to be investigated by future research.

#### REFERENCES

1. Frances A: Categorical and dimensional systems of personality diagnosis: a comparison. *Compr Psychiatry* 1982; 23:516-527
2. Frances A, Widiger TA: Methodological issues in personality disorder diagnosis, in *Contemporary Directions in Psychopathology: Toward the DSM-IV*. Edited by Millon T, Klerman GL. New York, Guilford Press, 1986
3. Morey LC: Personality disorders in *DSM-III* and *DSM-III-R*: convergence, coverage, and internal consistency. *Am J Psychiatry* 1988; 145:573-577
4. Blashfield RK, McElroy RA: The 1985 journal literature on the personality disorders. *Compr Psychiatry* 1987; 28:536-546
5. Widiger TA, Frances A: The DSM-III personality disorders: perspectives from psychology. *Arch Gen Psychiatry* 1985; 42:615-623
6. Cloninger CR: A systematic method for clinical description of personality variants: a proposal. *Arch Gen Psychiatry* 1987; 44:573-588
7. Leary T: *Interpersonal Diagnosis of Personality*. New York, Ronald Press, 1957
8. Shrout PE, Fleiss JL: Intraclass correlations: uses in assessing rater reliability. *Psychol Bull* 1979; 86:420-428
9. Mellsop G, Varghese F, Joshua S, et al: The reliability of axis II of *DSM-III*. *Am J Psychiatry* 1982; 139:1360-1361



# Effects of Methylphenidate on Early Adolescent Growth

Jennifer Vincent, M.D., Christopher K. Varley, M.D.,  
and Patti Leger, A.R.N.P., M.N., C.S.

*Thirty-one hyperactive adolescents treated with methylphenidate for at least 6 months demonstrated no significant deviation from expected height and weight growth velocities. In contrast to findings in prepubertal children, these results suggest that early adolescent growth is insensitive to methylphenidate.*

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Methylphenidate, a stimulant medication frequently used in the management of attention-deficit hyperactivity disorder, has been reported to have growth-suppressant effects in children. Some studies have suggested a temporary falling off from weight and height percentiles, with a possible period of growth rebound, or accelerated growth velocity, after the first year of treatment (1). Others have described growth inhibition only after 2 or more years of treatment (2). Recent reports have proposed that stimulant use during childhood has no significant impact on adult height and weight (3).

An increased awareness of the persistence of treatment-responsive attention-deficit hyperactivity disorder into adolescence has prompted an upsurge in methylphenidate use in this age group (4, 5). At the same time, critical scrutiny of psychostimulant use has intensified, with particular concern raised regarding potential adverse effects (6). Clearly, a considered approach to methylphenidate use in the adolescent age group, focusing on safety as well as efficacy, is warranted.

Methylphenidate's influence on early adolescent growth velocities has not been widely studied. Preclinical studies of methylphenidate-treated rats have observed a temporary falling off from height and weight percentiles in prepubertal but not adolescent animals (7).

The present study reviewed serial measurements of height and weight in methylphenidate-treated adoles-

cents. Its purpose was to describe the impact of methylphenidate on the rapid growth velocities of early adolescence (the growth spurt), which peak between 11.5 and 15.0 years (8).

## METHOD

### Subjects

The records of a university-affiliated outpatient child psychiatry service were reviewed for all patients with a diagnosis of attention-deficit hyperactivity disorder who received methylphenidate continuously for at least 6 months at some time after their 12th birthday. Thirty-one adolescents (25 boys and six girls) who met these criteria were identified. At the starting time of data collection, the mean $\pm$ SD age of subjects was 12.9 $\pm$ 0.8 years.

Subjects had been evaluated by the method described by Varley and Trupin (9), including clinical interview of the adolescent and family, focused neurological examination, the Conners Abbreviated Teacher Rating Scale, the Conners Abbreviated Parent Rating Scale, and a double-blind, placebo-controlled methylphenidate trial. Each subject met *DSM-III* criteria for attention-deficit disorder with hyperactivity and had no other major medical illnesses. The total duration of methylphenidate treatment, including the study period, ranged from 6 months to 6 years, 11 months: 15 subjects received medication for 6-12 months, nine subjects for 1-4 years, and seven subjects for 5-7 years. Analysis of age, gender, dose, and other characteristics on the basis of length of treatment was not feasible because of sample size.

The mean $\pm$ SD daily dose of methylphenidate received during the observation period was 34 $\pm$ 14 mg, or 0.75 $\pm$ 0.29 mg/kg of body weight. Subjects were treated steadily, without drug holidays. Boys and girls did not differ significantly in age or dose.

### Procedure

Two measurements of height and weight, 6-12 months apart (mean $\pm$ SD 221 $\pm$ 57 days), were recorded for each subject. Subjects were measured in indoor clothing and stocking feet on a platform scale. Measurements were noted by the treating clinician;

Received May 5, 1989; revision received Sept. 28, 1989; accepted Oct. 31, 1989. From the Division of Child Psychiatry, Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle. Address reprint requests to Dr. Vincent, Children's Hospital and Medical Center, 4800 Sand Point Way, N.E., Seattle, WA 98105.

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TABLE 1. Expected and Observed Heights and Weights of 31 Hyperactive Adolescents Treated With Methylphenidate

Item	Height				Weight			
	Measure (cm)		Percentile		Measure (kg)		Percentile	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Expected	158.7	10.2	50.7	31.1	48.1	10.6	46.5	28.9
Observed	158.7	9.8	50.3	30.1	47.9	10.3	46.3	29.1

weight was determined to the nearest 0.1 kg, and height to the nearest centimeter. Percentile ranks were assigned to the initial height and weight points (time 1) by using age- and sex-matched tables from the National Center for Health Statistics (8). These percentile ranks were extrapolated to the date of the second set of growth measures (time 2) and the corresponding height and weight identified as "expected" values for time 2. The difference between the expected and observed (i.e., measured) height and weight at time 2 was calculated for each subject. Initial measurements were randomly distributed throughout the year so as to eliminate any seasonal effects.

## RESULTS

Table 1 presents data on expected and observed height and weight measurements for the 31 hyperactive adolescents at time 1 (percentile) and time 2 (measure). Paired-samples two-tailed *t* tests demonstrated no significant difference between expected and observed height at time 2 for the group as a whole ( $t = -0.19$ ,  $df = 30$ ,  $p < 0.85$ ) or between expected and observed weight at time 2 for the group as a whole ( $t = -0.52$ ,  $df = 30$ ,  $p < 0.61$ ).

## DISCUSSION

The results of this retrospective study suggest that methylphenidate use, at customary doses (4, 10), does not noticeably impair early adolescent growth velocities over 6–12 months of treatment. This finding contrasts with reports of at least temporary methylphenidate-induced growth suppression in children and may indicate that early adolescent growth is relatively insensitive to methylphenidate administration. The results for this group are consistent with those reported for methylphenidate-treated laboratory animals (7).

Given the current level of concern regarding potential adverse effects of the medication, it is important that the preliminary findings reported here be substantiated and replicated with larger sample sizes and longer time intervals. This would permit analyses of sex differences and variation in growth effects with daily dosage (especially at higher doses) and cumulative dosage and elicit those effects which may emerge only after longer periods of treatment. On the basis of the findings presented here, it appears that heightened concern regarding the effects of methylphenidate on growth may not be warranted for the adolescent hyperactive population.

## REFERENCES

1. Satterfield JH, Cantwell DP, Schell A, et al: Growth of hyperactive children treated with methylphenidate. *Arch Gen Psychiatry* 1979; 36:212–217
2. Martes JA, Gittelman R: Growth of hyperactive children on maintenance regimen of methylphenidate. *Arch Gen Psychiatry* 1983; 40:317–321
3. Klein RG, Mannuzza S: Hyperactive boys almost grown up, III: methylphenidate effects on ultimate height. *Arch Gen Psychiatry* 1988; 45:1131–1134
4. Varley CK: Effects of methylphenidate in adolescents with attention-deficit disorder. *J Am Acad Child Psychiatry* 1983; 22:351–354
5. Safer DJ, Krager JM: A survey of medication treatment for hyperactive/inattentive students. *JAMA* 1988; 260:2256–2258
6. Shaywitz SE, Shaywitz BA: Increased medication use in attention-deficit hyperactivity disorder: regressive or appropriate? *JAMA* 1988; 260:2270–2272
7. Pizzi WJ, Rode EC, Barnhart JE, et al: Differential effects of methylphenidate on the growth of neonatal and adolescent rats. *Neurol Teratol* 1987; 9:107–111
8. Hamill PVV, Drizd TA, Johnson CL, et al: Physical growth: National Center for Health Statistics percentiles. *Am J Clin Nutr* 1979; 32:607–629
9. Varley CK, Trupin EW: Double-blind assessment of stimulant medication for attention deficit disorder: a model for clinical application. *Am J Orthopsychiatry* 1983; 53:542–547
10. Klorman R, Coons HW, Borgstedt AD: Effects of methylphenidate on adolescents with a childhood history of attention deficit disorder, I: clinical findings. *J Am Acad Child Adolesc Psychiatry* 1987; 26:363–367

# Weight Gain Associated With Clozapine

Seth Cohen, M.D., John Chiles, M.D., and Amy MacNaughton, R.N., C., B.S.N.

*Six of seven patients treated with clozapine gained 6–69 lb. Because of clozapine's anticipated availability in the United States, clinicians should be aware of this possible side effect, which, to the authors' knowledge, has not been reported previously.*

(Am J Psychiatry 1990; 147:503–504)

Clozapine, an atypical antipsychotic drug, holds promise for the treatment of refractory schizophrenia, for negative symptoms of this illness, and for schizophrenic patients with tardive dyskinesia. Its side effect profile is rather benign except for possible agranulocytosis, which has a cumulative incidence of 2% after a year of treatment. The most frequent adverse reactions noted by Kane et al. (1) included drowsiness, tachycardia, constipation, dizziness, and salivation. Weight gain is a troublesome side effect associated with typical neuroleptics but was not seen in Kane et al.'s study, nor, as far as we know, has it been reported anywhere else in the literature.

Because it is anticipated that clozapine will soon be available in the United States, the clinician should be aware of new side effects as they manifest themselves. Of the seven schizophrenic patients we have treated with clozapine, six gained weight, substantial amounts in five cases. Weight was monitored by means of initial and serial measurements during the patients' clinic appointments.

## CASE REPORTS

**Case 1.** Ms. A, a 26-year-old white woman, had a diagnosis of chronic schizophrenia, disorganized type. She had previously been treated with thiothixene and tiopirone (an investigational atypical neuroleptic) without weight gain. While taking chlorpromazine, she gained 40 lb. While taking clozapine (maximum dose, 400 mg/day) for 9 months, she gained 69 lb (from 140 to 209 lb). Her ideal body weight was 127–141 lb (2).

**Case 2.** Ms. B, a 23-year-old white woman, had been diagnosed as having chronic schizophrenia, paranoid type. She had been treated previously with perphenazine and haloperidol without weight gain. While taking trifluoperazine, she gained 15 lb. While taking clozapine (maximum dose, 550 mg/day) over 4½ months, she gained 17 lb (from 116 to 133 lb). Her ideal body weight was 111–124 lb.

**Case 3.** Mr. C, a 22-year-old white man, had a diagnosis of chronic schizophrenia, disorganized type. He had been previously treated with thioridazine, perphenazine, trifluoperazine, thiothixene, and molindone and had not gained weight. He received clozapine (maximum dose, 300 mg/day) for 2 months and gained 6 lb (from 157 to 163 lb). His ideal body weight was 141–160 lb.

**Case 4.** Mr. D, a 26-year-old white man, had a diagnosis of chronic schizophrenia, residual type. He had been previously treated with fluphenazine and tiopirone without weight gain. While taking clozapine (maximum dose, 175 mg/day) for 7½ months, he gained 17 lb (from 167 to 184 lb). His ideal body weight was 149–168 lb.

**Case 5.** Ms. E, a 31-year-old white woman, had a diagnosis of chronic schizophrenia, undifferentiated type. She had been treated previously with chlorpromazine, thioridazine, haloperidol, trifluoperazine, thiothixene, fluphenazine, loxapine, molindone, and tiopirone without weight gain. While taking clozapine (maximum dose, 500 mg/day) for 9 months, she gained 21 lb (165 to 186 lb). Her ideal body weight was 134–151 lb.

**Case 6.** Ms. F, a 45-year-old white woman, had been diagnosed as having chronic schizophrenia, undifferentiated type. Previously she had been treated with chlorpromazine, mesoridazine, trifluoperazine, thiothixene, fluphenazine, haloperidol, loxapine, molindone, and tiopirone without weight gain. While taking clozapine (maximum dose, 600 mg/day) for 7 months, she gained 18 lb (from 185 to 203 lb). Her ideal body weight was 137–155 lb.

**Case 7.** Ms. G, a 29-year-old white woman, had a diagnosis of chronic schizophrenia, undifferentiated type. She had previously been treated with chlorpromazine, perphenazine, trifluoperazine, thiothixene, haloperidol, acetophenazine, molindone, and tiopirone without weight gain. She took clozapine (maximum dose, 500 mg/day) for 4 months and did not gain weight (from her initial 191 lb). Her ideal body weight was 155–176 lb.

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## DISCUSSION

We have treated seven patients with clozapine over the past 2 years, and six have gained weight. These patients had taken clozapine for 2 to 9 months (mean, 6.5 months) and gained from 6 to 69 lb (mean, 24.7 lb). Four of our patients had started taking clozapine while at weights in their ideal ranges (cases 1–4) but exceeded those ranges while taking clozapine. However, the magnitude of patient 3's weight gain (6 lb) was unimpressive. The other two patients who gained weight (patients 5 and 6) each started taking clozapine while weighing more than the maximum ideal weight and then gained a significant amount of additional weight. Our patients had been previously treated with two to nine neuroleptics; one patient had gained 40 lb while taking chlorpromazine, and another had gained 15 lb while taking trifluoperazine. They reported no weight gain with any other neuroleptic. To our knowledge, ours is the first report of weight gain associated with clozapine.

Neuroleptics have serotonergic- and noradrenergic-blocking effects, which could lead to weight gain (3). Amidsen (4) reported that 80% of his patients treated with oral chlorpromazine gained weight and were at least 5% over their ideal weights and that the weights of 25% of the patients were excessive. Harris and Eth

(5) found weight gains in 85% of their patients treated with chlorpromazine, 82% of those treated with thiorixene, and 38% of those treated with fluphenazine. Weight loss has been reported with molindone (another atypical neuroleptic) and is hypothesized to be an anorexigenic effect of the medication (6).

Clozapine is not associated with tardive dyskinesia, causes few extrapyramidal symptoms, and is a treatment option for patients refractory to the typical neuroleptics. Our experience with a small sample of patients indicates it might cause the same weight gain seen with the typical neuroleptics.

## REFERENCES

1. Kane J, Honigfeld G, Singer J, et al: Clozapine for the treatment-resistant schizophrenic. *Arch Gen Psychiatry* 1988; 45:789–796
2. New weight standards for men and women. *Stat Bull Metrop Insur Co* 1959; 40:1
3. Silverstone T, Goodall E: The clinical pharmacology of appetite suppressant drugs. *Int J Obes* 1984; 8(suppl 1):23–33
4. Amidsen A: Drug produced obesity: experiences with chlorpromazine, perphenazine and clopenthixol. *Dan Med Bull* 1984; 11:182–189
5. Harris E, Eth S: Weight gain during neuroleptic treatment. *Int J Nurs Stud* 1981; 18:171–175
6. Gardos G, Cole JO: Weight reduction in schizophrenics by molindone. *Am J Psychiatry* 1977; 134:302–304

# Vitamin E in the Treatment of Tardive Dyskinesia

Ahmed M. Elkashef, M.B.B.Ch., Paul E. Ruskin, M.D.,  
Norman Bacher, M.D., and David Barrett, M.D.

*Eight subjects with persistent tardive dyskinesia were treated with vitamin E and placebo in a randomized, double-blind crossover study. Their mean score on the Abnormal Involuntary Movement Scale (AIMS) was significantly lower after treatment with vitamin E than after placebo administration.*

(Am J Psychiatry 1990; 147:505–506)

**T**ardive dyskinesia is a common, often irreversible side effect of neuroleptic medication. Although a number of psychopharmacologic treatments have been tried to alleviate this side effect, no effective treatment has been found (1).

It has been theorized that persistent tardive dyskinesia is caused by free radical toxicity in the basal ganglia (2). This toxicity leads to destabilization of neuronal membranes through lipid peroxidation (3). Neuroleptic medications have been shown to increase, at least initially, the turnover of catecholamines, especially dopamine, in the brain (4). Increased dopamine metabolism could lead to greater production of cytotoxic free radicals. Vitamin E, with its antioxidant properties, could neutralize the damaging effects of these free radicals (5, 6). Thus, vitamin E might be an effective treatment for tardive dyskinesia. Its side effects are usually mild and well tolerated. They include nausea, vomiting, abdominal cramps, diarrhea, headache, fatigue, and, if there is a history of allergy, skin rash.

A recent double-blind crossover study demonstrated the efficacy of vitamin E in the treatment of tardive dyskinesia (7). The current study replicates that finding.

## METHOD

Outpatients at a Veterans Administration mental hygiene clinic were recruited for the study. The inclu-

sion criteria were a *DSM-III-R* diagnosis of schizophrenia or schizoaffective disorder, a research diagnosis of tardive dyskinesia (8), and an age between 18 and 75 years. The exclusion criteria were significant medical illness, history of allergy to vitamin E, and pregnancy. The diagnosis of tardive dyskinesia was made by two independent raters using the Abnormal Involuntary Movement Scale (AIMS) (9).

Ten patients met the criteria and signed informed consent statements. Two did not complete the study; one patient was noncompliant and the other experienced substantial side effects (nausea) while taking placebo. The mean  $\pm$  SD age of the remaining eight patients was  $56.6 \pm 12.0$  years. Seven were male, and one was female. All of the subjects had taken neuroleptics for at least 15 years, and their tardive dyskinesia had been diagnosed  $3.8 \pm 2.8$  years previously (for two patients the initial date of diagnosis was unknown).

The study lasted 10 weeks. Constant doses of all nonprotocol medication were maintained throughout the study. All but one of the subjects (patient 1) were taking neuroleptic medication. During the first 2 weeks of the study, all subjects were observed while taking their current medications. The subjects were then assigned in a random, double-blind manner to either vitamin E or placebo for 4 weeks, after which they crossed over to the other treatment for a second 4-week period. The dose of vitamin E was 400 IU/day for the first week, 400 IU b.i.d. for the second week, and 400 IU t.i.d. for the final 2 weeks. The subjects were evaluated biweekly by a blind trained rater using the AIMS and the Brief Psychiatric Rating Scale (BPRS) (10). Placebo-drug differences were examined with repeated measures analysis of variance (ANOVA).

## RESULTS

As shown in table 1, the AIMS scores were significantly lower after treatment with vitamin E (mean  $\pm$  SD =  $6.75 \pm 3.90$ ) than after placebo administration ( $8.56 \pm 3.25$ ) ( $F = 6.21$ ,  $df = 1, 6$ ,  $p < 0.05$ ). A carryover or order effect was ruled out ( $F = 0.20$ ,  $p > 0.05$ ). We chose a 30% reduction in AIMS score as the criterion for good response to vitamin E. Five of the eight patients had reductions of 30% or more from baseline. Patients with buccolingual movements (patients 2–4) or with dystonia in addition to the dyskinesia (patient

Received June 27, 1989; revision received Sept. 22, 1989; accepted Oct. 31, 1989. From the Department of Psychiatry, Baltimore VA Medical Center. Address reprint requests to Dr. Elkashef, Institute of Psychiatry and Human Behavior, University of Maryland School of Medicine, 645 West Redwood St., Baltimore, MD 21201.

Hoffman-La Roche, Inc., supplied the drug and placebo for this study.

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TABLE 1. AIMS Scores of Eight Patients With Tardive Dyskinesia in Crossover Study of Vitamin E and Placebo

Patient	Medication		First Condition <sup>a</sup>	AIMS Score		
	Neuroleptic	Anticholinergic or Other		Baseline	After Vitamin E	After Placebo
1	None	None	Placebo	9.0	3.5	9.0
2	Perphenazine 12 mg/day	None	Vitamin E	6.0	4.0	4.5
3	Fluphenazine, 7.5 mg/day	Propranolol, 80 mg/day	Placebo	8.0	5.0	6.0
4	Thioridazine, 150 mg/day	None	Vitamin E	10.0	6.0	6.5
5	Thioridazine, 100 mg/day	None	Vitamin E	9.0	5.5	8.5
6	Haloperidol, 40 mg/day	Cyproheptadine, 8 mg/day	Vitamin E	6.5	6.0	8.5
7	Haloperidol, 4 mg/day	Benztropine, 4 mg/day	Placebo	14.0	13.5	13.0
8	Thiothixene, 20 mg/day	Benztropine, 2 mg/day	Vitamin E	13.0	10.5	12.5

<sup>a</sup>The baseline severity of tardive dyskinesia was closely matched in the two groups. The two patients who dropped out received placebo first.

1) improved the most. One patient experienced mild diarrhea, which lasted for 2 days and resolved spontaneously while the patient continued to take the drug. The BPRS scores did not show any significant changes.

## DISCUSSION

Although conclusions based on such a small sample must be made with caution, our results replicate the findings of Lohr et al. (7). Both studies demonstrate the efficacy of vitamin E in the treatment of tardive dyskinesia.

These studies involved patients with long-standing tardive dyskinesia. If vitamin E works by neutralizing the toxic effects of free radicals in the brain, then vitamin E might also be effective if used prophylactically, to prevent neuronal damage before it occurs. Additional research is indicated to further elucidate the role of vitamin E in the treatment and prevention of tardive dyskinesia.

## REFERENCES

1. Jeste DV, Wyatt RJ: Understanding and Treating Tardive Dyskinesia. New York, Guilford Press, 1982
2. Cadet JL, Lohr JB, Jeste DV: Free radicals and tardive dyskinesia. *Trends in Neuroscience* 1986; 9:107-108
3. Cohen G: Oxyradical toxicity in catecholamine neurons. *Neurotoxicology* 1984; 5:77-82
4. Mackay AVP, Iversen LL, Rossor M, et al: Increased brain dopamine and dopamine receptors in schizophrenia. *Arch Gen Psychiatry* 1982; 39:991-997
5. Cadenos E, Ginsberg M, et al: Evaluation of alpha-tocopherol antioxidant activity. *Biochem J* 1986; 223:755-759
6. Oske FA: Vitamin E, a radical defense. *N Engl J Med* 1980; 303:454-455
7. Lohr JB, Cadet JL, Lohr MA, et al: Alpha-tocopherol in tardive dyskinesia (letter). *Lancet* 1987; 1:913-914
8. Schooler NR, Kane JM: Research diagnoses for tardive dyskinesia (letter). *Arch Gen Psychiatry* 1982; 39:486-487
9. Guy W (ed): ECDEU Assessment Manual for Psychopharmacology: Publication ADM 76-338. Washington, DC, US Department of Health, Education, and Welfare, 1976, pp 534-537
10. Overall JE, Gorham DR: The Brief Psychiatric Rating Scale. *Psychol Rep* 1962; 10:799-812



# Surreptitious Drug Use by Patients in a Panic Disorder Study

Duncan B. Clark, Ph.D., M.D., C. Barr Taylor, M.D.,  
Walton T. Roth, M.D., Chris Hayward, M.D., M.P.H., Anke Ehlers, Ph.D.,  
Jürgen Margraf, Ph.D., and W. Stewart Agras, M.D.

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*In a double-blind, placebo-controlled trial comparing alprazolam and imipramine for panic disorder, serum analysis revealed that a substantial proportion of the patients took explicitly prohibited anxiolytic medication. Excluding these patients changed the results.*  
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While the psychological aspects of the placebo effect have been extensively analyzed and discussed (1) and surreptitious drug use has been noted in panic disorder research patients (2), the possibility that some placebo responders may be surreptitiously taking prohibited medications has not been addressed. When subjects' taking prohibited medications is acknowledged as a potential problem, experimenters usually rely on the patients themselves to report their use of these medications (3). The purpose of this study was to determine, by serum analysis, the frequency of surreptitious medication use in a placebo-controlled drug trial for panic disorder, to characterize patients who took prohibited medication, and to test whether or not inclusion of these patients changed the results. A more detailed report of the results with regard to cardiovascular side effects and clinical outcome is in press (4).

## METHOD

Seventy-nine outpatients were recruited through the mass media to participate in a study comparing pharmacologic treatments for panic disorder. The mean  $\pm$  SD age of the patients was  $35.1 \pm 9.2$  years; 21 (27%) were male and 58 (73%) were female. They were given the Structured Clinical Interview for DSM-III (5), medical histories were taken, and physical examinations, routine blood and urine tests, and thyroid func-

tion tests were performed. Patients were eligible for the study if they had at least some spontaneous panic attacks, had panic attacks with four symptoms occurring during an attack, or had had at least one panic attack each week for the past 3 weeks. Patients were excluded if they had diagnoses of primary affective disorder, alcohol or drug abuse, psychosis, or obsessive-compulsive disorder or if they were acutely suicidal, pregnant, or lactating or had a significant medical disorder. The procedures for the study were fully explained, and informed consent was obtained.

All patients were asked to be drug free for at least 2 weeks before baseline assessment and to take only prescribed study medication during treatment. Blood samples were taken and clinical measures were obtained for all patients at baseline and after 4 and 8 weeks of treatment. The serum analyses were for imipramine, desmethylinipramine, diazepam, desmethyldiazepam, and alprazolam; the results were available after all patients had completed the study.

Panic attacks and phobic avoidance were selected as the primary outcome measures. The mean number of panic episodes per week was determined from patient diaries and included anticipatory, situational, spontaneous, and limited-symptom panic attacks (6). A clinical measure of phobic avoidance was derived from questions from the Marks-Matthews Fear Inventory (7), with two added items (i.e., feeling trapped or caught in closed places and fear of being left alone). Data on a variety of other clinical measures were also collected.

Of the 79 patients beginning treatment, 26 were randomly assigned to placebo, 27 to imipramine, and 26 to alprazolam. Medications were dispensed in identical capsules of placebo, alprazolam (1 mg), or imipramine (30 mg). Medication was increased until patients were free of panic attacks, suffered from unpleasant side effects, or were taking 10 tablets per day. The average daily doses of medications at the end of 8 weeks of treatment were 3.7 (range=1-8) mg of alprazolam and 147 (range=30-270) mg of imipramine.

## RESULTS

At baseline 17 (22%) of the 79 patients were found by serum analysis to have measurable blood levels of

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**TABLE 1. Study Completion Rates and Changes in Symptoms of 79 Panic Disorder Patients Who Did or Did Not Comply Fully With Their Prescribed Regimens in an 8-Week Drug Trial**

Condition	Completers <sup>a</sup>		Change in Number of Panic Attacks per Week <sup>b</sup>		Change in Avoidance Score <sup>c</sup>	
	N	%	Mean	SD	Mean	SD
Noncompliers included in analysis						
Placebo (N=26)	20	77	-3.3	10.9	-3.2	4.0
Imipramine (N=27)	22	81	-5.9	4.5	-4.9	6.5
Alprazolam (N=26)	24	92	-7.5	7.4	-4.2	4.0
Noncompliers excluded from analysis						
Placebo (N=26)	15	58	0.4	11.7	-2.8	4.4
Imipramine (N=27)	17	63	-5.6	4.1	-5.4	7.0
Alprazolam (N=26)	23	88	-7.7	7.5	-4.5	4.1

<sup>a</sup>Four patients with very low serum levels of prohibited medication at baseline and no other violations of the protocol were included here as completing the study. When noncompliers were included, there were no significant differences between conditions ( $\chi^2=2.4$ ,  $df=1$ , n.s.); when noncompliers were excluded, there was a significant difference between the alprazolam condition and the imipramine and placebo conditions ( $\chi^2=6.7$ ,  $df=1$ ,  $p<0.05$ ).

<sup>b</sup>Active medication was compared with placebo by one-tailed  $t$  test. When noncompliers were included, there were no significant differences between conditions ( $F=1.5$ ,  $df=2$ , 62, n.s.); when noncompliers were excluded, there were significant differences between conditions ( $F=4.3$ ,  $df=2$ , 48,  $p<0.02$ ); for imipramine versus placebo,  $t=1.92$ ,  $df=27$ ,  $p<0.05$ ; for alprazolam versus placebo,  $t=2.52$ ,  $df=33$ ,  $p<0.01$ .

<sup>c</sup>When noncompliers were included, there were no significant differences between conditions ( $F=0.6$ ,  $df=2$ , 53, n.s.); when noncompliers were excluded, there were again no significant differences between conditions ( $F=0.8$ ,  $df=2$ , 40, n.s.).

prohibited medication. Twelve had serum that was positive for diazepam and/or desmethyldiazepam, two for alprazolam, and three for desmethylimipramine. These serum-positive patients showed significantly higher phobic avoidance scores at baseline than the patients who were serum negative (mean $\pm$ SD=12.0 $\pm$ 5.6 and 7.9 $\pm$ 6.0, respectively;  $t=2.39$ ,  $df=71$ ,  $p<0.02$ ) but were not significantly different on frequency of panic attacks (9.0 $\pm$ 5.2 and 7.3 $\pm$ 6.0, respectively;  $t=1.04$ ,  $df=77$ , n.s.). Of these 17 patients, five dropped out of the study and eight used prohibited medication while completing the study. The remaining four patients had either very low serum levels of diazepam and desmethyldiazepam (<100 ng/ml; N=3) or a low serum level of desmethyldesipramine (25.1 ng/ml; N=1) and otherwise completed the study without violating the protocol. Thus, only 24% (four of 17) of the serum-positive patients completed the protocol without using prohibited medication, a significantly smaller percentage than the 84% (N=52) of the 62 patients who were serum negative at baseline ( $\chi^2=20.5$ ,  $df=1$ ,  $p<0.0001$ ).

During treatment, six patients in the placebo condition, four in the imipramine condition, and one in the alprazolam condition took prohibited medication. All but one of these patients completed the study. Of the patients assigned to the placebo condition, one patient had serum that tested positive for alprazolam, two for tricyclics, and two for both desmethyldiazepam and tricyclics. One placebo patient had serum that was positive for desmethyldiazepam at week 4 but dropped out before completing the study. Of those assigned to the imipramine condition, four patients had serum that tested positive for desmethyldiazepam. One patient assigned to the imipramine group had a serum imipramine level of zero and was therefore also considered to have violated the protocol. Of the patients assigned to

alprazolam, one patient had serum that was positive for desmethyldiazepam.

The results of the study, including and excluding noncompliant patients, are presented in table 1. For this analysis, patients whose serum tested positive for prohibited medication at baseline and/or during treatment and one patient who did not take the prescribed medication (i.e., whose imipramine level was zero) were considered to be "noncompliers" except where noted. When noncompliant patients were included, there were no significant differences between drug conditions in completion rate, change in frequency of panic attacks, or change in phobic avoidance. When treatment noncompliers were excluded, the completion rate was significantly lower for patients taking placebo and imipramine than for those taking alprazolam. Excluding all noncompliant patients, those in the imipramine and alprazolam conditions showed greater change in panic attack frequency than those taking placebo, but there were no significant differences in change in phobic avoidance. Four of the five placebo patients who completed the study while taking prohibited medication reported that they had no panic attacks at the endpoint of treatment.

## DISCUSSION

A rather large proportion of patients in this study (i.e., 20 of 79 patients, or 25%) had serum that tested positive for prohibited medication during the "drug-free" baseline period and/or during the time they were supposed to be taking the assigned study medications. In four of these cases, it is possible that the patients discontinued medications as directed and, because of the relatively long half-lives of desmethyldiazepam (30–200 hours) (8) and desmethylimipramine (14–62 hours) (8), still had detectable levels of these active

metabolites. On the other hand, some patients may have taken alcohol, illicit drugs, or prescription medications other than those tested. Baseline noncompliers had more severe phobic avoidance than compliers and may have been reluctant to discontinue needed anxiolytic medication. Other patients may have found their study medication ineffective and therefore believed it necessary to add to their treatment.

This result suggests that the placebo response seen in some subjects in panic disorder research (9) may result from undetected surreptitious drug use. In our study, use of prohibited medication was apparently less important in the active medication conditions, as there was little impact in these groups on treatment outcome. Because only panic disorder patients were included, the findings cannot be generalized to research concerning other psychiatric disorders. Nevertheless, these results suggest that screening of urine or serum for relevant medications is necessary during all drug trials and that researchers should insist that patients have negative drug screens before being assigned to treatment conditions. Most of the patients who were serum positive at baseline either dropped out or continued to take prohibited medication throughout the study, indicating that in future studies it may be necessary to exclude some patients. However, noncompliance may be lessened if patients are aware that they are being monitored. The elimination of surreptitious drug

use by research patients would remove an important uncontrolled variable and, therefore, might allow researchers to conduct studies with smaller sample sizes.

#### REFERENCES

1. Hovarth P: Placebos and common factors in two decades of psychotherapy research. *Psychol Bull* 1988; 104:214-225
2. Sheehan DV, Coleman JH, Greenblatt DJ, et al: Some biochemical correlates of panic attacks with agoraphobia and their responses to a new treatment. *J Clin Psychopharmacol* 1984; 4: 66-75
3. Roth WT, Telch MJ, Taylor CB, et al: Autonomic characteristics of agoraphobia with panic attacks. *Biol Psychiatry* 1986; 21:1133-1154
4. Taylor CB, Hayward C, King R, et al: Cardiovascular and symptomatic reduction effects of alprazolam and imipramine in patients with panic disorder: results of a double-blind placebo-controlled trial. *Psychiatry Res* (in press)
5. Spitzer RL, Williams JB: Structured Clinical Interview for DSM-III, Upjohn Version. New York, New York State Psychiatric Institute, Biometrics Research, 1983
6. Taylor CB, Sheikh J, Agras WS, et al: Ambulatory heart rate changes in patients with panic attacks. *Am J Psychiatry* 1986; 143:478-482
7. Marks IM, Matthews AM: Brief standard self-rating for phobic patients. *Behav Res Ther* 1979; 17:263-267
8. Hollister L: *Clinical Pharmacology of Psychotherapeutic Drugs*. New York, Churchill Livingstone, 1983
9. Coryell W, Noyes R: Placebo response in panic disorder. *Am J Psychiatry* 1988; 145:1138-1140



# Evidence for Physical and Psychological Dependence on Anabolic Androgenic Steroids in Eight Weight Lifters

Kirk J. Brower, M.D., George A. Eliopoulos, M.D., Frederic C. Blow, Ph.D.,  
Donald H. Catlin, M.D., and Thomas P. Beresford, M.D.

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*All eight users of anabolic androgenic steroids in a pilot survey of weight lifters reported withdrawal symptoms and continued steroid use despite adverse consequences. Psychiatric (especially, depressive) symptoms were prominent in dependent users, underscoring the importance of diagnosing steroid dependence in clinical practice.*

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Anabolic androgenic steroids are synthetic derivatives of testosterone that are used to enhance athletic performance or physical appearance (1). The increasing use of these drugs (2) has resulted in increasing reports of adverse medical and psychiatric effects (3–7). Organic mood disorders, psychoses, aggression, and suicidal tendencies have been reported (4–7), and steroid-associated fatalities or near fatalities from myocardial infarctions, stroke, and liver disease have also occurred (3).

Most steroid-using athletes and bodybuilders obtain their drugs illicitly (1, 2). The doses taken by such users typically exceed the therapeutic doses prescribed for legitimate medical conditions (such as male hypogonadism) by 10- to 100-fold (1, 5). To achieve these high doses, several steroids are taken in combination, a practice known as “stacking” (1, 5, 6). Oral and intramuscular forms of steroids are also combined (1), which has led to needle sharing. These patterns of illicit use tend to increase the health risks of taking anabolic androgenic steroids.

Many athletes continue using steroids, despite the risks, because they are misinformed about the risks or

they believe that the risks are worth taking for the potential benefits. Another possibility is that some athletes become psychologically and/or physically dependent on steroids and thus are unable to stop using them. However, we are aware of only two documented cases, and no systematic studies, of anabolic androgenic steroid dependence reported in the professional literature (6, 7). In the absence of more data, some writers have raised the question of whether these drugs are truly addictive (8).

This question has important implications for prevention and treatment. If steroids have addictive potential, then all concerned individuals need to be properly informed. Moreover, individuals who are unable to stop using steroids despite the adverse consequences or despite their desire to stop might best be referred for specialized substance abuse treatment. Thus, psychiatrists and other clinicians would need to assess their high-risk patients (athletes and weight lifters) for dependence on steroids (6). Finally, substance abuse treatment providers would need to accommodate, and target their programs to, the special needs of steroid abusers as these become better understood.

We report some pilot data that are consistent with the hypothesis that the use of anabolic androgenic steroids can result in drug dependence.

## METHOD

Subjects for this study were eight weight lifters who were identified by contact persons (gym owners [N=3], health care providers [N=2], or acquaintances [N=3]) as either current or past users of anabolic androgenic steroids. Subjects were asked by their contact persons to complete a questionnaire, designed to be self-administered in 15–20 minutes, requesting information about demographics, weight lifting patterns, and patterns of steroid use. Questions for eliciting information on symptoms of psychoactive substance dependence, based on the *DSM-III-R* criteria (pp. 165–185), were included.

Subjects known to the authors were assured of confidentiality, and subjects not known to us were assured of anonymity. All subjects were instructed not to put their names on the questionnaires. Anonymity was en-

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Received May 23, 1989; revision received Sept. 6, 1989; accepted Sept. 13, 1989. From the Alcohol Program and the Alcohol Research Center, Department of Psychiatry, University of Michigan School of Medicine, and the Paul Ziffren Olympic Analytical Laboratory, Department of Pharmacology, UCLA School of Medicine, Los Angeles. Address reprint requests to Dr. Brower, University of Michigan Medical Center, UH8D8806/0116, 1500 East Medical Center Dr., Ann Arbor, MI 48109.

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TABLE 1. Patterns of Use of and Dependence on Anabolic Androgenic Steroids in Eight Weight Lifters

Subject	Age at Last Use (years)	DSM-III-R Criterion Symptoms Present <sup>a</sup>	Duration of Use (months)	Number of Drugs Taken at One Time	Withdrawal Symptoms
1	24	6, 8	52	1	Decreased sex drive
2	52	2, 5, 6, 8	76	3	Decreased sex drive, fatigue, dissatisfaction with body image
3	40	1, 6, 8	26	3	Decreased sex drive, fatigue, depression, insomnia, suicidal thoughts
4	35	6, 8	89	3	Fatigue, insomnia, restlessness, lack of interest
5	26	1, 2, 6, 8	29	2	Fatigue, depression, dissatisfaction with body image, headaches, anorexia, desire for more steroids
6	65	3, 6, 8	104	1	Insomnia, desire for more steroids
7	29	1-3, 6-8	96	>5	Fatigue, dissatisfaction with body image, anorexia, desire for more steroids
8	23	1-3, 5-8	42	4	Decreased sex drive, fatigue, depression, dissatisfaction with body image, anhedonia, headaches, restlessness, insomnia, anorexia, lack of interest, desire for more steroids

<sup>a</sup>The DSM-III-R criteria for psychoactive substance dependence are summarized as follows: 1) more substance taken than intended, 2) desire yet inability to cut down or control substance use, 3) large time expenditure on substance-related activity, 4) frequent intoxication or withdrawal symptoms when expected to function or when physically hazardous, 5) social, work, or leisure activities replaced by substance use, 6) continued substance use despite problems caused or worsened by use, 7) tolerance, 8) withdrawal symptoms, 9) substance used to relieve or avoid withdrawal symptoms.

sured by having the subject insert the completed questionnaire in a preaddressed, stamped envelope that was mailed directly to us, without returning it first to the contact person.

Three subjects were interviewed following completion of their questionnaires to determine whether their answers corresponded to the intent of the questions. One of these subjects also underwent urine testing to confirm his history of steroid use (9). From this we concluded that the data from the questionnaires were generally valid.

## RESULTS

All subjects were male, and their mean  $\pm$  SD age was  $38.6 \pm 14.9$  years. The mean age at the time of last use was  $36.8 \pm 15.0$  years (range=23–65). All subjects reported at least two symptoms of dependence, including continued steroid use despite adverse consequences (DSM-III-R criterion 6) and withdrawal effects (criterion 8) (see table 1). Regarding adverse consequences, seven of the eight subjects admitted that they continued using steroids despite psychological problems such as feeling nervous, irritable, or depressed; five of the eight cited adverse social consequences, and only three cited physical problems. Withdrawal symptoms reported by three or more subjects included depression, fatigue, decreased sex drive, insomnia, anorexia, dissatisfaction with body image, and the desire to take more steroids (table 1).

Subjects had used steroids from 2–10 years. Most users "cycled" by taking the steroids for 6–12 weeks

and then abstaining for 1–24 weeks, a pattern that is common among steroid users (1, 2). All but two subjects used two or more steroids in combination (see table 1), and all but one subject had used both injectable and oral steroids.

## DISCUSSION

All eight steroid users in our pilot study reported symptoms of dependence that were consistent with DSM-III-R criteria. Six subjects met the DSM-III-R criteria for dependence, which is defined as having at least three criterion symptoms. Every subject met DSM-III-R criterion 6 for psychoactive substance abuse by reporting continued steroid use despite adverse consequences. (In DSM-III-R, psychoactive substance abuse is conceptualized as a less severe condition than dependence and is diagnosable when either of the following is present: recurrent drug use when this is physically hazardous or presence of symptoms meeting criterion 6 for drug dependence.) All eight subjects also reported withdrawal symptoms (criterion 8). Since withdrawal symptoms are regarded as evidence of physical dependence, and DSM-III-R criterion symptoms 1–6 indicate psychological dependence, our data suggest that both physical and psychological dependence can occur with use of anabolic androgenic steroids.

Psychiatric symptoms were prominent in our sample. Most subjects reported that they continued to use steroids despite the adverse consequences of feeling nervous, irritable, or depressed. Similarly, the with-

drawal symptoms frequently reported by our subjects—depression, fatigue, decreased sex drive, insomnia, anorexia, and dissatisfaction with body image—are commonly seen in patients with mood disorders and eating disorders. Indeed, all eight subjects reported at least one psychiatric symptom as part of either criterion 6 (use despite adverse consequences) or criterion 8 (withdrawal symptoms). Thus, athletes and bodybuilders who complain of psychiatric symptoms need to be assessed carefully for steroid use and dependence (4–6).

The data provide limited information about the patterns of steroid use that lead to dependence. Subjects 3 and 5, who combined injectable and oral steroids for less than 3 years, were judged to be dependent. However, dependence also occurred in subject 6, who took just one drug orally at three times the therapeutic dose (methandrostenedione, 15 mg/day) but did this nearly continuously for nearly 9 years. Thus, dependence may develop more rapidly in users who combine high doses of oral and injectable forms of steroids, but taking only one drug by mouth does not necessarily protect against dependence.

Although young men are generally at highest risk for illicit steroid use (2), our sample suggests that some relatively older men also use steroids (subjects 2, 3, and 6). The symptoms and patterns of steroid use reported by the older subjects did not appear to differ from those of the younger subjects.

Our study was limited by the small number of subjects and the use of anonymous self-reports. Nevertheless, the wide range in age among our subjects indicates that different types of steroid users were represented in our sample. Moreover, most of the sub-

jects were not selected from treatment settings and, thus, did not necessarily have severe cases of drug dependence. Finally, self-reported data from the questionnaires were confirmed by clinical interview in three cases and by urine testing in one case.

This pilot study provides additional evidence that anabolic androgenic steroids can produce dependence (6, 7). Psychiatrists and others need to consider this diagnosis, especially when evaluating avid weight lifters who have depressive symptoms (5). Further study is needed to determine the predictors and mechanisms of steroid dependence and to develop optimal treatment strategies.

#### REFERENCES

1. Wilson JD: Androgen abuse by athletes. *Endocr Rev* 1988; 9: 181–199
2. Buckley WE, Yesalis CE, Friedl KE, et al: Estimated prevalence of anabolic steroid use among male high school seniors. *JAMA* 1988; 260:3441–3445
3. Kibble MW, Ross MB: Adverse effects of anabolic steroids in athletes. *Clin Pharm* 1987; 6:686–692
4. Brower KJ, Blow FC, Eliopoulos GA, et al: Anabolic androgenic steroids and suicide (letter). *Am J Psychiatry* 1989; 146:1075
5. Pope HG Jr, Katz DL: Affective and psychotic symptoms associated with anabolic steroid use. *Am J Psychiatry* 1988; 145: 487–490
6. Brower KJ, Blow FC, Beresford TP, et al: Anabolic-androgenic steroid dependence. *J Clin Psychiatry* 1989; 50:31–33
7. Tennant F, Black DL, Voy RO: Anabolic steroid dependence with opioid-type features (letter). *N Engl J Med* 1988; 319:578
8. Cowart VS: If youngsters overdose with anabolic steroids, what's the cost anatomically and otherwise? *JAMA* 1989; 261: 1856–1857
9. Hatton CK, Catlin DH: Detection of androgenic anabolic steroids in urine. *Clin Lab Med* 1987; 7:655–668



# Effect of Distraction on Communication Failures in Schizophrenic Patients

Ann Phillips Hotchkiss, Ph.D., and Philip D. Harvey, Ph.D.

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*Manic, schizophrenic, and normal subjects were interviewed in the presence and absence of distracting information, and their speech performance was evaluated. Normal and manic subjects were unaffected by irrelevant information. Schizophrenic subjects manifested more reference failures during distraction than during nondistraction periods.*

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It has been relatively well demonstrated that schizophrenic patients are distracted by the presence of irrelevant information (1, 2), and several studies (1-3) have found that distractibility correlates with severity of thought disorder, measured both linguistically and clinically. One problem in the interpretation of these cross-sectional results is that they only demonstrate that distractible schizophrenic subjects also often have a communication disorder. The common hypothesis (4) that speech failures in schizophrenia occur during high-load periods of information processing has not been directly tested by these studies.

This report presents the results of a study in which concurrent irrelevant stimuli of various types were inserted into a conversation. That methodology enabled direct measurement of the influence of distracting information on speech performance, measured linguistically through comparison of competent and incompetent speech produced under conditions of distraction and nondistraction. We used a linguistic measure of thought disorder because it could be measured in relatively short speech segments without bias and because it has repeatedly been found to correlate highly with severity of clinical thought disorder in schizophrenia (5). Manic and normal comparison samples were in-

cluded to examine whether any deficits in speech performance were specific to schizophrenia.

## METHOD

The psychiatric subjects were 17 schizophrenic and 14 manic patients selected from consecutive admissions to a state psychiatric center. Diagnostic information was collected with the Schedule for Affective Disorders and Schizophrenia (6), and diagnoses were made according to *DSM-III* criteria. All of the schizophrenic patients were receiving neuroleptics, and the manic patients were receiving neuroleptics, lithium carbonate, or both. A group of 15 normal control subjects was selected for similarity to both patient samples and screened for personal or familial histories of psychiatric care. The three subject groups did not differ significantly in sex distribution ( $\chi^2=4.64$ ,  $df=2$ ), age ( $F=0.78$ ,  $df=2$ , 43), or years of education ( $F=1.59$ ,  $df=2$ , 43), and the two patient groups did not differ significantly in number of prior admissions ( $t=0.83$ ,  $df=29$ ).

Four minutes of three distraction conditions (white noise, random words, and text) were audiotaped at a maximum volume of 60-70 dB, making six counter-balanced sequences of the three distraction conditions. A 2-minute block of silence (i.e., nondistraction) was added to the beginning and end of each tape to examine performance without interfering stimuli. The distraction text came from excerpts of sixth-grade science texts, read aloud by a male voice. The distraction words were randomly selected from the text distraction passages and were read by the same voice at the rate of one every three seconds.

The interviewer and subject spoke into separate directional microphones. The output from the two microphones and the tape-recorded stimuli went into a microphone mixer and then into an amplifier, to which headphones for the subject were attached. The output of the tape recorder and both microphones was calibrated to be of identical volume before each subject was tested.

Each subject was interviewed the day after diagnostic assessment by a research assistant who followed a structured interview that avoided clinical topics. During this interview, the subject wore headphones and

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**TABLE 1. Speech Performance of 17 Schizophrenic, 14 Manic, and 15 Normal Subjects During Distraction and Nondistraction Conditions**

Measure and Condition	Schizophrenic Subjects		Manic Subjects		Normal Subjects	
	Mean	SD	Mean	SD	Mean	SD
Verbal references <sup>a</sup>						
Nondistraction	0.44	0.18	0.43	0.11	0.43	0.09
Distraction	0.39	0.07	0.43	0.09	0.39	0.07
Reference failures <sup>a</sup>						
Nondistraction	0.12	0.14	0.09	0.06	0.08	0.07
Distraction	0.20 <sup>b</sup>	0.14	0.13	0.10	0.06	0.03

<sup>a</sup>Number of occurrences per clause.<sup>b</sup>Significantly different from the nondistraction condition ( $p < 0.05$  by simple effects test).

was exposed to a randomly assigned tape; the conversation between the interviewer and subject was tape recorded.

Two linguistic variables in the subjects' speech—reference failures and verbal references—were evaluated by two raters from transcripts of the tape-recorded interviews. Reference failures consisted of unclear or ambiguous references to previously presented verbal information. Explicit verbal references were references in speech that referred to previous verbal information through the use of comparatives, pronominals, or other forms. The reliability of the ratings ( $\kappa$ ) was 0.91 for reference failures and 0.94 for explicit verbal references. The transcripts were labeled for the time intervals corresponding to the particular distraction conditions; the dependent variable for each of the two reference patterns was the number of occurrences per clause.

## RESULTS

Initial analyses were conducted to compare the frequency of the reference variables in the initial and final 2-minute nondistraction blocks and across the three different distraction conditions. These analyses revealed no differences across the various conditions for either reference variable. The frequencies of the reference variables were then averaged across the three distraction conditions into a single score, and the two 2-minute nondistraction segments were summed into a single score. The subjects' frequencies for the two reference variables during distraction and nondistraction, presented as a function of the number of occurrences per clause, are shown in table 1.

A 3 (Diagnosis)  $\times$  2 (Distraction/Nondistraction) repeated measures analysis of variance was used to examine each of the two reference variables. For verbal references there were no significant main effects or interactions. For reference failures there was a significant two-way interaction between diagnosis and condition ( $F = 4.06$ ,  $df = 2, 43$ ,  $p < 0.05$ ) and a significant main effect of diagnosis ( $F = 6.62$ ,  $df = 2, 43$ ,  $p < 0.01$ ). Sim-

ple effects tests found that the schizophrenic subjects, but not the normal and manic subjects, produced significantly more incompetent references per clause during distraction than during nondistraction. The main effect of diagnosis was followed up with Tukey tests, which revealed that the schizophrenic subjects produced significantly more incompetent references overall than did the normal control subjects ( $p < 0.05$ ) but did not differ from the manic patients in this respect. The manic patients did not differ significantly from the normal subjects in frequency of reference failure.

## DISCUSSION

There was an effect of distraction on discourse in the schizophrenic subjects: the patients became more disorganized in their speech while communicating in the presence of distraction, suggesting that overload conditions can cause increases in communication disorder. Manic patients also became slightly, but not significantly, more disorganized during distraction, suggesting that the effect was not completely specific to schizophrenic patients. An interesting finding was that white noise, independent of textual or even verbal characteristics, caused increases in communication disorder. It is possible, therefore, that overload theories that posit specific verbal interference effects of information overload (4) may be overspecific. In fact, perceptual load alone appears to be able to disorganize the speech of schizophrenic patients, which suggests that verbal information-processing models of language failure may in fact be overly elaborate.

In another recent study (3), schizophrenic patients manifested a decrement in their ability to shadow textual organization during distraction. Across the two studies it appears that sensory overload during discourse monitoring and generation leads to language dysfunction in schizophrenic subjects, as indexed by increases in reference failures. These data are likely to be affected by the medication received by the patients, including the manic comparison subjects. Given earlier results suggesting that susceptibility to distraction is responsive to medication (2, 7), it is likely that the patients' medication reduced the magnitude of the distraction effects in this study. A follow-up study is underway to examine the effect of medication on this procedure.

## REFERENCES

1. Harvey PD, Earle-Boyer EA, Levinson JC: Cognitive deficits and thought disorder: a retest study. *Schizophr Bull* 1988; 14: 57-66
2. Oltmanns TF, Ohayon J, Neale JM: The effect of medication and diagnostic criteria on distractibility in schizophrenia. *J Psychiatr Res* 1979; 14:81-91
3. Wielgus MS, Harvey PD: Dichotic listening and recall in schizophrenia and mania. *Schizophr Bull* 1988; 14:689-700
4. Maher BA: A tentative model of schizophrenic utterance, in

- Progress in Experimental Personality Research, vol 12. Edited by Maher BA. New York, Academic Press, 1983
5. Harvey PD: Speech competence in manic and schizophrenic psychoses: the association between clinically rated thought disorder and cohesion and reference performance. *J Abnorm Psychol* 1983; 92:368-377
  6. Spitzer RL, Endicott J: Schedule for Affective Disorders and Schizophrenia (SADS), 3rd ed. New York, New York State Psychiatric Institute, Biometrics Research, 1977
  7. Strauss ME, Lew MF, Coyle JT, et al: Psychopharmacologic and clinical correlates of attention in chronic schizophrenia. *Am J Psychiatry* 1985; 142:497-499



## Book Forum

Nancy C. Andreasen, M.D., Ph.D., Editor

### TEXTBOOKS

*Concise Guide to Clinical Psychiatry*, by Steven L. Dubovsky, M.D. Washington, D.C., American Psychiatric Press, 1988, 192 pp., \$16.95 (paper).

*Concise Guide to Consultation Psychiatry*, by Michael J. Wise, M.D., and J.R. Rundell, M.D. Washington, D.C., American Psychiatric Press, 1988, 175 pp., \$15.95 (paper).

*Concise Guide to Somatic Therapies in Psychiatry*, by Lawrence B. Guttmacher, M.D. Washington, D.C., American Psychiatric Press, 1988, 151 pp., \$16.95 (paper).

These three pocket-size productions derive from the work of Dr. Robert Hales, editor of the Concise Guides series. As he notes in each introduction, the guides can fit into a lab coat and are especially aimed at medical students and residents. These approximately 4-by-6-inch non-spiral-bound guides are admittedly limited in their content and referencing and are meant to complement lengthier texts. They all use *DSM-III-R* and are as convenient and compact as they purport to be.

*Concise Guide to Clinical Psychiatry* by Dr. Dubovsky is the most comprehensive of the lot. I was initially skeptical of what could be provided in such a small package claiming such a broad domain. Yet he accomplishes his goal of providing clinically useful material, without theory, using a consistent design in every chapter. Each chapter covers the epidemiology, signs and symptoms, present and past and family history, associated problems and laboratory findings, course, etiology, differential diagnosis, and treatment of a given disorder. The chapters are all remarkably informative and pragmatic and demonstrate the author's capacity to distill what is central to understanding and treating each disorder. There is simply no fat to his presentation. For trainees on an inpatient rotation, the author's design of one chapter on psychosis, rather than separate and more developed chapters on schizophrenia and affective psychoses, may not be adequate. Psychosocial interventions are provided in all chapters and reveal a cognitive-behavioral approach to patients and families.

Drs. Wise and Rundell's *Concise Guide to Consultation Psychiatry* begins with a fine schema of what a consultation is and how it should be rendered. This clear and precise exposition on consultation, however, does not deal as well with the liaison aspects of this psychiatric specialty. The authors provide one of the best compilations of scales, tests, evaluation instruments, and mnemonics I have seen. There is also an excellent breakdown of drug actions and interactions and a fine discussion on pain and analgesics. The authors minimally discuss psychosocial aspects of patient care, emphasizing ward management and biological processes instead.

*Concise Guide to Somatic Therapies in Psychiatry* by Dr. Guttmacher opens with an important set of principles to guide the clinician in pharmacological decision making. The

chapter on ECT is excellent, especially for such an abbreviated text. However, the design of this guide is confusing, with chapters on categories of drugs and chapters on particular disorders. Although there is a good discussion of pharmacokinetics, I was surprised not to see more on drug interactions. The role of alcohol and other substances in the etiology of psychiatric disorders is underrepresented in the text.

The Concise Guide series accomplishes its goals of conciseness, utility, and convenience. However, there is considerable overlap if one purchases several of the books. The overlap comes in the areas of biological and descriptive psychiatry, leaving the reader without a written resource for the dynamic and social aspects of human disorder. Purchase of the series, therefore, presents a quandary for the debt-laden medical student or house officer. For the price of several Concise Guides, the trainee could purchase a comprehensive text or a modest text plus a psychopharmacology handbook. Like the poor student heading off to Europe for the first time on a limited budget, one might like to purchase books specific to each country on the continent but may be able to afford only a single, more universal travel guide.

LLOYD I. SEDERER, M.D.  
Cambridge, Mass.

*Modern Perspectives in Clinical Psychiatry*, edited by John G. Howells, M.D. New York, Brunner/Mazel, 1988, 392 pp., \$40.00.

This is number 10 in the Modern Perspectives in Psychiatry series, each of which is theme-oriented and multiauthored. Some readers, like myself, are more familiar with the series logo, an upward pointing arrow, than with its title. The first book in the series came out in 1967, and new volumes used to appear annually—until they began to appear occasionally. Number 9 was published in 1981.

*Modern Perspectives in Clinical Psychiatry* contains 17 review articles. As promised by the editor, the philosophies of the authors and their subject matters are eclectic; topics include psychiatric epidemiology, acquired immune deficiency syndrome (AIDS), lithium, the borderline patient, Alzheimer's disease, toxic psychosis, subcortical dementias, computer applications, emergency psychiatry, and epilepsy.

My favorite chapters include the following. "The Premenstrual Syndromes" suggests that a number of psychiatric disorders not ordinarily associated with menses can be exacerbated by it. "DSM-III: An Evaluation" surveys criticism on *DSM-III* in the English-language literature. "Brain Imaging Techniques" explains the new technologies, describes data accumulated over 10 years, and soberly concludes that there is as yet no breakthrough in our understanding of "functional illness."

I found out some interesting tidbits for which I wish there was a question-and-answer period to offer further explana-

tion. The chapter on liaison psychiatry mentions that our medical colleagues in primary care and family practice postgraduate programs do not use psychiatrists as consultants, instead calling in psychologists and social workers. The chapter on attention deficit disorder mentions that our British colleagues, who are definitely interested in pharmacotherapy, rarely make this diagnosis and rarely prescribe stimulants to children.

In most of the chapters, the writing and editing are above average and the bibliographies are excellent. I was disappointed with a few chapters, however. I was skeptical of a chapter by community psychiatrists in Italy describing how they will close down all of their psychiatric hospitals. Another chapter bemoaned how hardly anyone in our profession (except the authors of the chapter) has written papers applying Von Bertalanffy's systems theory to psychiatry.

Just as a good child may not meet its parents' expectations, so too does this volume fall short of what the editor proposes. The 10 volumes in the Modern Perspectives series do not meet the editor's description of being "an international encyclopedia of psychiatry." They survey some, but not all, areas of psychiatry and offer neither systematic access nor a comprehensive index.

The book does update the psychiatrist, as the editor proposes, but the chapters in this 1988 volume appear to have been written in 1986. Thus, the AIDS chapter offers only six references.

Readers who like well-written review articles will like this book. Everyone should find something of interest here, but the topics are so varied that few will find every chapter of equal interest.

JOHN HOCHMAN, M.D.  
Tarzana, Calif.

*Companion to Psychiatric Studies*, 6th ed., edited by R.E. Kendell, M.D., F.R.C.P., F.R.C.Psych., and A.K. Zealley, F.R.C.P.(Edin.), F.R.C.Psych. New York, Churchill Livingstone, 1988, 828 pp., \$96.00.

Immediately upon opening *Companion to Psychiatric Studies*, I found that this is no ordinary textbook. The first image, preceding the title page, is a set of four 1847 drawings of patients with melancholia and mania. Between the preface and the list of contributors is an extract from the annual report of the Royal Edinburgh Asylum for the Insane for the year 1887, listing "causes of insanity." The suggestion that this volume is consistent with our stereotyped view of British medicine and psychiatry as firmly rooted in history is reinforced as one begins to read the opening chapter, "Historical Introduction." Almost every comprehensive text in the field pays lip service to the historical roots of modern psychiatry; this chapter truly informs the reader. Starting with an unusually perceptive analysis of the myth of Cupid and Psyche, the author, T. Walmsley, guides us through the early medicine of Hippocrates and Galen, the mysticism of Maxwell and Swedenborg, and the neurology of Pinel and Jackson to the dawning of modern psychiatry in the era of James, Freud, and Sullivan. No mere chronology, this review is seamless and complex.

"Charming," the reader may be tempted to judge, "another retrospective masterpiece from our transatlantic cousins." Such a conclusion is utterly unwarranted, for the textbook that unfolds is a true delight—informative, readable, and contemporary. Its title is a bit self-effacing, since, as the ed-

itors acknowledge, it is "as comprehensive in its scope and as catholic in its orientation as the confines of a single volume will allow."

The organization and selection of chapters are fairly standard for a general text: eight introductory chapters covering history and the basic sciences, four chapters on diagnosis, 18 chapters on psychopathology, four chapters on psychiatry in different settings, and eight chapters covering psychiatric therapies. The content of these chapters, however, is truly impressive. Since this edition follows its immediate predecessor by only 5 years, it is remarkably up-to-date in its presentation of neuroscience and psychobiology. These contributions review neuroanatomy and neurophysiology briefly without sacrificing depth; details are selected to be particularly relevant to the student or practitioner of clinical psychiatry. There is probably no other text that does this fine a job of integrating biological, psychological, and social determinants of human development and behavior.

The U.S. psychiatrist, having practiced with the official absence of neuroses for almost a decade, may be put off by the lengthy chapter on "Neurotic Disorders." The author, C.P. Freeman, explains that these disorders will remain in ICD-10 despite their exclusion from DSM-III, reviews them as a class, then discusses the individual entities. He is quite successful in bridging the conceptual gap between the diagnostic schemes, and his clinical descriptions are all consistent with DSM-III phenomenologic classifications. His chapter on "Personality Disorders" puts most others to shame. He begins by outlining approaches to classification of personality disorders: type, trait, and psychodynamic, situational, and interactionist approaches. He then presents models for understanding the relationships between personality disorders and psychiatric illness. The clinical descriptions are augmented by a sophisticated analysis of the multiple views of the borderline concept. Like most other authors in this volume, Freeman compares and evaluates competing models without apparent prejudice.

The chapters on therapies are nearly all characterized by lucid guidelines for the selection of therapies and an attention to technical instruction. There are some worthwhile inclusions here that are missing from most textbooks. A.W. Clare's chapter, "Individual Psychotherapies," reviews carefully the topic of outcome assessment. The chapter on "Counselling and Crisis Intervention" by J. Greenwood and J. Bancroft presents in practical form an important aspect of psychiatric practice too often relegated to a few superficial paragraphs on supportive psychotherapy. "Psychiatric Rehabilitation" by J.A.T. Dyer returns to the psychiatrist's domain the concept of truly comprehensive treatment planning.

The flaws in this work are relatively minor. The presentation of the individual chapters makes their internal organization somewhat confusing. Sections of different weight are listed under comparable headings; it would be difficult to outline many of the chapters. Similarly, there is a lack of parallel structure between parallel chapters. But these criticisms are picky. They are apparent only in contrast to the many strengths of this book, and correcting them might even have robbed the best chapters of some of their individual brilliance.

Indeed, the editors have succeeded laudably at the most difficult of their tasks, the attainment of singularity of purpose. Multiauthored textbooks usually have all the focus of a variety show. Not this one. There is consistency of information across all chapters; the authors never contradict one another, and there is precious little redundancy for a work of this size. The reader can follow an unbroken thread of rele-

vance from the first principles of neurochemistry, to the psychobiology of mental disorders, to the phenomenology of clinical entities, to the biopsychosocial formulation of treatment strategies.

The editors, aware that general psychiatry textbooks are most popular among candidates for membership in the Royal College of Psychiatrists, modestly express the hope that their book "will also be read by psychiatrists who are no longer faced with the need to pass examination, and that it will be useful to a wider readership." It certainly deserves such a place. *Companion to Psychiatric Studies* is full of important information presented in a thoughtful and readable fashion. It is a delightful volume that will reward the reader for every trip to its well-considered chapters.

DAVID BIENENFELD, M.D.  
Cincinnati, Ohio

## HOMOSEXUALITY

**The Psychoanalytic Theory of Male Homosexuality**, by Kenneth Lewes, Ph.D. New York, Simon & Schuster, 1988, 285 pp., \$19.95.

Freud knew that there were many things he did not know about male homosexuality. He looked forward to having his theories added to by contributions not only from psychoanalysis but also from biological sciences. Over several decades, and notably including his three essays on the theory of sexuality, the Schreber case, and his work on Leonardo da Vinci, he considered several partial and unintegrated theories about some aspects of homosexuality. Dr. Lewes lists and discusses four of these theories as Freud's major ones. However, although Freud considered that male homosexuality involved an arrest in sexual development, he did not consider it an illness; he felt it was no advantage but that it was nothing to be ashamed of and should not be classified as an illness. Freud also thought there was little likelihood of changing homosexuals into heterosexuals and (a touchy point for psychoanalysts) that homosexuals could be psychoanalysts. He advised Jones to judge psychoanalytic candidates on their other qualities. Jones did not agree, and his view has prevailed nearly everywhere. (Shortly before she died, Jeanne Lampl de Groot told me that the Dutch psychoanalytic society accepted homosexual analysts and was, as far as she knew, the only psychoanalytic society to do so.)

Freud did at times blur some issues later usefully separated by others, such as gender-related behavior and sexual behavior, but generally his theories and attitude were tentative, humane, and respectful. He greatly admired the homosexual subjects of two of his major biographical essays, and he explicitly had Plato, Leonardo, and Michelangelo in mind when allowing that there was more to homosexuality than was represented by homosexual patients.

Several of Freud's points and attitudes were developed and others were lost or contradicted by many later psychoanalysts. Especially in what was probably the era of the greatest prestige of psychoanalysis, just after World War II, there was a prominent strain in psychoanalysis of allocating to or assuming major pathology in homosexuality. That strain became rather generalized, going well beyond specific theoretical constructs about some forms of homosexuality and entering a series of psychological areas such as narcissism, masochism, paranoia, superego development, passivity, oral-

ity, close-binding mothers and distant fathers, and preoedipal separation-individuation. Some of that generalized strain remains, protected, Dr. Lewes and others think, by the reluctance of psychoanalysis to look at and integrate nonpsychoanalytic data.

Dr. Lewes, like Dr. Richard Friedman and other recent students of homosexuality, conveys how little psychoanalysis has been able to use relevant data from, for example, sociological, psychological, animal, twin, adoption, endocrine, and gender-disorder studies. As one prominent example, he documents how little psychoanalysis acknowledged the Kinsey report. Similarly, Dr. Lewes shows how, in the wake of the very influential 1962 study of Bieber et al., psychoanalysis made rather little use of other careful studies of groups of male homosexuals such as those of Hooker, Bell and Weinberg, and Saghir and Robins. There are risks in being uneducated outside the boundaries of psychoanalysis itself, and male homosexuality is an example of several of those risks.

Dr. Lewes reminds us that a wide array of studies, including psychoanalytic ones, were taken into account in APA's decision in 1973 to delete homosexuality from *DSM-II*. Some analysts were startled by the decision, even if analysts in fact spoke on both sides of the change: Stoller and Marmor prominently in favor of deleting the diagnosis, Socarides and Bieber against. Dr. Lewes favors the arguments of Stoller and Marmor (1) and criticizes their opponents for continuing to extrapolate from homosexual patients to all homosexuals.

Dr. Lewes can be a bit too drily egalitarian, as when he discusses a checkerboard of oedipal possibilities, but he can also use dry parallels as well, as when he pertinently compares psychoanalysis and homosexuality with psychoanalysis and women. He notes the helpfulness to analysis of female analysts commenting on and helping to create psychoanalytic theories of women and the probable detriment to psychoanalysis of not having explicitly homosexual analysts comment on the (often remarkably similar) psychoanalytic theories of homosexuality.

Dr. Lewes has written a useful book—useful both as a history of science (in this case, of psychoanalytic theory on one topic over many decades) and as a history of much complex, influential, and inconclusive thinking about homosexuality. In his fairly detailed gathering and rereading of the analytic literature of the past 80 years or so, of particular interest to those familiar with recent literature will be views of several earlier authors (Sadger, Boehm, Rank, Sachs, Ferenczi, Brill) and some of the subtleties of subsequent theorists such as Glover, Bak, Bychowski, Khan, and Gillespie. The views of Socarides and Bieber are far more familiar (Socarides has been relatively assertive and prolific). Dr. Lewes notes how widespread their views are but remains quite skeptical about their validity. He reserves his greatest disapproval, however, for their predecessor, an analyst whose prolific writings appeared in the 1940s, 1950s, and 1960s, had wide influence, and probably did considerable harm to many homosexuals and to psychoanalysis: E. Bergler. Lewes quotes Bergler as saying, "I have no bias against homosexuality . . . [but] homosexuals are essentially disagreeable people . . . [displaying] a mixture of superciliousness, false aggression, and whimpering, . . . subservient when confronted with a stronger person, merciless when in power, unscrupulous about trampling on a weaker person" (p. 15).

That Dr. Lewes includes and explicates the ideas of some writers he considers wrong is a reasonable and proper part of a history of science. However, he less justifiably leaves out a few important analysts for, to my mind, inadequate reasons:



Jung, Fromm, and Stekel are out for not being "strictly analytic," but Melanie Klein, for example, is repeatedly in. On a different level, one particularly interesting new analytic voice on the subject of male homosexuality, Richard Isay, is also left out, although Isay began publishing in *The Psychoanalytic Study of the Child* 3 years before Dr. Lewes's book was published.

The book is not particularly easy to read, but it provides a very useful service in reviewing a long, complex, and interesting area of psychoanalytic literature. As a history of analytic thought in this one area, the book can stand on its own. As a study about thinking about homosexuality, however, I think the book might well be supplemented, and I urge the interested reader to read it alongside the books of Richard Friedman (2) and Richard Isay (3).

#### REFERENCES

1. Marmor J (ed): *Homosexual Behavior: A Modern Reappraisal*. New York, Basic Books, 1980
2. Friedman RC: *Male Homosexuality: A Contemporary Psychoanalytic Perspective*. New Haven, Yale University Press, 1988
3. Isay RA: *Being Homosexual: Gay Men and Their Development*. New York, Farrar Straus Giroux, 1989

LAWRENCE HARTMANN, M.D.  
Cambridge, Mass.

**Male Homosexuality: A Contemporary Psychoanalytic Perspective**, by Richard C. Friedman, M.D. New Haven, Conn., Yale University Press, 1988, 288 pp., \$35.00.

Filling a gap in the review and update of psychoanalytic thinking on male homosexuality, this book provides an analysis of how psychoanalytic thinking on a specific subject evolved and explores the resistance to changes in psychoanalytic thinking in the face of clinical evidence and research.

The book offers some fresh viewpoints and some new insights into male homosexuality, incorporating and, at times, ignoring data and clinical materials gathered since the turn of the century. The author approaches male homosexuality without assuming that it is a mental illness per se, in line with the thinking of most psychiatrists and APA but not most psychoanalysts.

In part one, Friedman very carefully outlines new biopsychosocial research and statistics, deploring the past psychoanalytic tendencies to extrapolate from small numbers and to ignore data that did not fit into the assumptions being asserted—especially in his analysis of the much quoted but very flawed work of Bieber. At times, however, Friedman draws conclusions himself or makes generalizations that contradict the very process he deplores. After carefully reviewing studies of childhood gender identity and gender role disturbances and noting that only a few gay men had such conditions as children, he concludes, without a statistical basis, that "absence of such disturbance diminishes the likelihood that a boy will become a man who is exclusively or predominately homosexual" (p. 47).

Like many clinicians who cannot fully grasp how members of the same sex can love and want to be sexual with each other and who mistakenly associate adult male homosexuality and effeminacy (more specifically, assuming that if a man wants to be sexual with another man he must be woman-like on some level), the author seems determined to make

childhood gender-discordant behavior, or at least the sense of "unmasculinity," a cause of homosexuality. He does not recognize that the child may well be homosexual to begin with due to genetics or the biological factors he so well describes, may feel different, and may be confused as to how to make sense of such "different" feelings and be accepted in the world. These differences may cause the father to reject the child out of discomfort or confusion and leave the child feeling more comfortable with people who accept him more easily—his mother, girls, teachers, or boys less focused on aggressive play.

The author goes to great pains to disassociate homosexuality and mental illness early in the book but then, perhaps unwittingly, defeats his goal in part two by describing male homosexuals in various diagnostic categories, focusing on the borderline and primitive conditions. It will take a sophisticated reader not to link homosexuality and these diagnoses. Friedman offers a helpful adaptation of a "diagnostic cube" with the Kinsey sexual orientation scale as one axis, the "psychostructural level" as another axis, and "predominant personality subtype" as another axis, reiterating that gay men do not have a higher rate of mental illness or characterological problems.

In part three the author writes an excellent review of developmental considerations in adolescence and a good review of childhood, except for the fixation on childhood effeminacy.

Part four consists of conclusions and speculations that require further research. The summary is very helpful, even if the conclusions must be understood in the light of the author's biases—namely, 1) that homosexuality, although not pathological per se, has clear psychodynamic origins with biological and endocrine components, 2) that effeminacy or unmasculinity are factors leading to adult homosexuality rather than that they are results of childhood homosexuality, and 3) that a homosexual orientation will definitely affect how certain psychopathological conditions get expressed. The book ends with a very useful discussion on the resistance of psychoanalytic thinking to change.

Almost nothing is said about homophobia, a profoundly insidious phenomenon affecting all gay people and a factor greatly influencing the full expression of homosexuality in adolescents and adults.

This book is a valuable addition to the literature on male homosexuality. Parallel efforts on understanding lesbianism are necessary. For a full picture of homosexuality, however, the reader will also want to consult the new book by Dr. Richard Isay (1), the collection by Drs. Stein and Cohen (2), and the review of current thinking on homosexuality in the January 1988 issue of *Psychiatric Annals* (3).

#### REFERENCES

1. Isay RA: *Being Homosexual: Gay Men and Their Development*. New York, Farrar Straus Giroux, 1989
2. Stein TS, Cohen CC (eds): *Contemporary Perspectives on Psychotherapy With Lesbians and Gay Men*. New York, Plenum, 1986
3. Cabaj RP (ed): *Sexuality and Homosexuality*. *Psychiatr Annals* 1988; 18(1)

ROBERT PAUL CABAJ, M.D.  
Brookline, Mass.

**Being Homosexual: Gay Men and Their Development**, by Richard A. Isay, M.D. New York, Farrar Straus Giroux, 1989, 149 pp., \$14.95.

Homosexuality and psychoanalysis have made peculiar bedfellows for much of this century. Gay men and women have sought help for an array of problems often not expressly linked to sexual orientation. Analysts have responded with uncertainty about homosexuality as an acceptable treatment outcome. The net result has been an unsteady alliance between patient and therapist with many instances of mutual disappointment.

In this book Richard Isay moves beyond this stalemate to present a bold revision of psychoanalytic thought on male homosexuality and a reformulation of the treatment of gay patients. Although primarily a compilation of papers and presentations, Isay's book moves smoothly from such topics as childhood and early homosexual identity to adult relationships of homosexual men, the impact of acquired immune deficiency syndrome (AIDS) on gay men, homoerotic fantasies in heterosexual men, and psychotherapy with gay men. The novelty of Isay's ideas, supported by references to clinical experience and research on the genetic and biological aspects of homosexuality, makes this a seminal work. This book is at once provocative, fair-minded, and enjoyable to read.

Isay squarely addresses the question of homosexuality as an acceptable treatment outcome. He argues that same-sex object choice should be accepted as a biologically based given for gay patients. Isay believes that adjustment to this predisposition—by both patient and family—is the key determinant of healthy psychological development in gay men. Departing from traditional theory, Isay sees "pathology" as an outgrowth of the stigma attached to being gay and rejects the view that intrinsic childhood pathology is the root of adult homosexuality.

In addition to theoretical considerations, Isay faults a pathological model of homosexuality on clinical grounds: he finds it undermines the therapeutic alliance and leads to technical errors. For example, a therapist may misinterpret a patient's regrets about childlessness as evidence of the "intrinsic pathology" of homosexuality or a wish to change sexual orientation. Isay writes that the patient is likely to perceive a therapist who makes this interpretation as unaccepting and, even worse, unempathic. As a practicing analyst, Isay regards a more open-minded application of analytic technique useful in working with gay patients: it can be usefully employed with these patients just as it is with heterosexual patients—to help them achieve more loving relationships and enhanced self-esteem.

Isay believes a perspective unencumbered by the pathological model also allows the therapist to better understand the contemporary experiences of gay men, such as their reactions to the human immunodeficiency virus (HIV) epidemic. In a chapter on the impact of AIDS on the development of healthy gay men and homophobia, he discusses how understandable fears about HIV can have a variety of meanings and serve other agendas besides risk reduction. This chapter is required reading for any therapist working with male homosexuals and is one of the few analytic explorations of the psychological effects of HIV infection on gay men.

If psychoanalytic theory of male homosexuality has been characterized by unanalyzed subjectivity and negative judgments (1), *Being Homosexual: Gay Men and Their Development* is a timely departure from this history and a welcome addition to recent scholarly efforts that relate psy-

choanalytic theory to the fields of genetics, psychoendocrinology, and sex research (2). I hope that this emerging trend includes more consideration of female homosexuality, which has carried the additional burden of being overlooked and understudied.

Perhaps Isay's book represents the inevitable reformulation of analytic thought as data are derived from a more open process of inquiry. Isay writes within an expanded frame of reference and challenges readers to reexamine their own understanding of male homosexuality. Underlying this book is a message that seems both self-evident and profound: our theory and treatment of homosexuality should be responsive to homosexuals and not to precepts that are self-perpetuating and detrimental to our patients' well-being.

#### REFERENCES

1. Lewes K: *The Psychoanalytic Theory of Male Homosexuality*. New York, Simon & Schuster, 1988
2. Friedman RC: *Male Homosexuality: A Contemporary Psychoanalytic Perspective*. New Haven, Yale University Press, 1988

ROBERT M. KERTZNER, M.D.  
New York, N.Y.

#### PSYCHOANALYSIS AND PSYCHOTHERAPY

**Understanding Psychotherapy: The Science Behind the Art**, by Michael Franz Basch. New York, Basic Books, 1988, 329 pp., \$19.95.

Many psychotherapists believe that they understand how psychotherapy "works." Frequently, they are able to persuade their patients; occasionally, they are also able to convince some of their colleagues.

There are two types of theory essential to psychotherapy. First is the theory of the therapeutic process, dealing with concepts such as alliance, resistance, transference, interpretation, and working through. Basch spends little time on this kind of theory, largely accepting traditional Freudian concepts with an admixture of the ideas of the late Heinz Kohut. He seems to regard the therapeutic process as an art rather than a domain for scientific inquiry. He is not interested in alternative models or in the systematic, scientific study of either the process of therapy or its results, perhaps because of his personal conviction that it is regularly successful: "I cannot think of a psychoneurotic patient who has accepted my recommendation for and participated in a psychoanalysis who has not had a creditable result" (p. 304). From the many clinical vignettes and case histories in this book, a reader would infer that Basch understands and has good results with virtually all of his patients. Many other therapists would not make such an inference about their own work, and the small amount of existing systematic research does not support this conclusion, but Basch does not address the discrepancy.

The second kind of theory that therapists need is the theory of whatever they believe to be the basis of mental life. For Freud, this was the biology of basic drives. For others, it has been interpersonal relationships, language and symbolic functioning, cognition and learning, or theories from a number of other disciplines. Some therapists draw on several of these, and others restrict the base of psychotherapy to one of them. Basch is clear, consistent, and rather narrow in this

regard. For him, "psychotherapy . . . is applied developmental psychology" (p. 29). Furthermore, the critical period of development is specific: "I would not consider seriously any explanation for mental functions whose roots cannot be inferred from observation or experimentation in the preverbal stages of life—those first two years or so" (p. 26). This is what he means by "the science behind the art." His developmental psychology is enriched with neurobiological and cybernetic reasoning. Basch constructs a theory of mental development that forms the basis for his understanding of patients and guides his therapeutic interventions. He does not discuss or critically appraise the scientific basis of this theory, the validity of its hypotheses, its methodologic problems, or its contradictory findings. By "science," he means the conclusions he reaches after reading the scientific literature; he does not mean a systematic method for testing ideas and assessing their validity.

The model of pathology and pathogenesis that emerges has several striking features. Pathology is always understood developmentally: "Whether a patient is suffering from a borderline state, a personality disorder, or a neurosis, for example, depends to a great extent on when the damage to his or her affective development occurred" (p. 128). Pathology also has a remarkably specific timetable: "The watershed for the character development of these [narcissistic and borderline] children comes around the age of six years or so" (p. 237). The reader has no way of knowing whether this is a fact accepted by other therapists, an inference from uncited research, or Basch's personal clinical impression.

Basch says that, generally, pathology develops because of parental failure. His patients tell stories and form transference relationships that suggest empathic lapses by their parents, and he regularly accepts these stories as evidence of actual failures in parental functioning. Freud made similar inferences from his patients' accounts of traumatic sexual experiences in childhood until, in 1897, he began to question whether such accounts might reveal more about the fantasy life of the patient than the facts of early development. Basch seems strangely unconcerned about this problem. He is aware of other potential determinants of psychopathology, but they seem to have little to do with his therapeutic strategy. He tends to make sweeping generalizations that are not accepted by others and that are offered with neither data nor discussion. For example: "Patients with a psychoneurosis tend to come from stable backgrounds that are neither confused nor confusing. Their families are embedded in a social milieu in which their place is clear" (p. 284). Statements such as this seem to be derived from his theory; they do not provide support for it.

Much of the text is given over to clinical vignettes. Basch writes well, and his accounts hold the reader's attention, although they seem somewhat stylized—everything fits and makes sense, and his interventions tend to be didactic and intellectualized. Developmental explanations are always found, and patients always respond to interventions based on them. He believes that psychiatric patients are basically different from borderline or narcissistic patients and that the appropriate clinical approach for them may be different from the very first contact. Basch has an astonishing confidence in his own instantaneous clinical judgment. He decides on the moment of meeting one of his patients that a certain reserve is desirable because the patient was appropriate for psychoanalysis, and indeed he prescribes that treatment during the initial interview.

Basch is an important thinker, a clear writer, and, based on the data in this book, a gifted clinician. In this book he

presents his model of psychotherapy and his view of personality development and psychodynamic psychopathology, on which it is based. He thinks of his psychological theories as "scientific" but presents them simply as a coherent developmental scheme without any discussion of the evidence for their validity. He has no interest in the scientific study of psychotherapy itself or in the competing theories of other therapists. He is generous in sharing descriptions of his clinical work, and his book offers a detailed view of the favorite theories of a gifted, serious, and scholarly psychotherapist and how they shape his therapeutic efforts.

ROBERT MICHELS, M.D.  
New York, N.Y.

**New Concepts in Psychoanalytic Psychotherapy**, edited by John Munder Ross, Ph.D., and Wayne A. Myers, M.D. Washington, D.C., American Psychiatric Press, 1988, 278 pp., \$32.00.

This book is a series of 14 good chapters. They are written by clinicians who know psychoanalytic theory as well as clinical phenomenology and are trying to link the theory to the phenomena. The chapters deal with cutting-edge problems—the issues of how to formulate a case in which there are deficits in capacity for functioning and conflicts in how to function. Thus, they deal with the more severe personality disturbances, those which are not quite psychotic but also not quite neurotic in the traditional formulations of psychoanalysis. The authors are a sturdy core of clinicians who are neither zealous in adherence to a single brand name within psychoanalytic theory nor restrictive in their approach to classical psychoanalytic technique. Rather, they deal in the broadly relevant matrix of psychoanalytic psychotherapy and offer a new kind of integration for what might constitute psychoanalytic formulation of a case even if seen only in consultation or supervision.

This book is a smorgasbord with something to appeal to anyone who already knows a fair amount about psychoanalytic psychotherapy. This is fair enough, because the dust jacket announces that the book is "intended to augment the knowledge of the psychoanalytically informed and interested clinician." It is not clear, however, why and how chapters were chosen. In their acknowledgments the editors thank the editors and organizers of various symposia and the editorial board of the *International Journal of Psychoanalytic Psychotherapy*. If these papers were published before, however, this is not indicated. Even the authors' acknowledgments at the end of the chapters thank various people for helping but do not say in what symposium the paper was presented or if and when it was published in the *International Journal of Psychoanalytic Psychotherapy*.

The editors introduce the book by stating that their aim is to demonstrate the applicability of the developmental and technical precepts of psychoanalysis to treatment, training, and educational situations beyond the confines of the couch. If the reader were to ask, "What are psychoanalytic clinicians up to these days?" this is just the book to provide the answer. I even imagine that I might offer this volume to Sigmund Freud for an evening if he came back to life and asked, "What's up?" and did not want to read a book with one domain.

The book is divided into three sections. The first, edited by Samuel Wagonfeld, has four interesting chapters on the origin and treatments of developmental deficits. The papers



range from borderline conditions and narcissism in adolescents to masochistic character formation and the reemergence of traumatic feeling states.

The second section, on consultation and supervision, has no immediate relationship to the first, but the volume editors have provided some structural continuity. The section on developmental deficits deals with masochistic character, and the section on consultation and supervision deals with masochistic character pathology in medical settings.

In a series of critiques of the theories of Otto Kernberg and Heinz Kohut, the third section deals with conflict versus deficit explanations of psychopathological personality patterns.

This is not a book for trainees or those who want an introduction. It will, however, give the experienced psychodynamic clinician new perspectives on theory, therapy, consultation, and supervision.

MARDI J. HOROWITZ, M.D.  
San Francisco, Calif.

**Six Steps in the Treatment of Borderline Personality Organization**, by Vamik D. Volkan, M.D. Northvale, N.J., Jason Aronson, 1987, 228 pp., \$25.00.

Dr. Volkan's book on the psychotherapy of borderline patients contains two main sections of equal length. One deals with theoretical issues, and the other is devoted to the description of his work with a particular borderline patient treated over some 6½ years.

The theoretical section is written from a purely psychoanalytic frame of reference. Volkan relies heavily on Freudian developmental theory as modified by Mahler and on object relations theory. Volkan's own formulations are based on his work with nine "psychosis prone" patients whose borderline conditions appeared to have stemmed from one of three types of abnormal early environment. The first involves inadequate mothering, including situations where the mother is burdened with another pregnancy during the first year of the patient's life. "In such cases," Volkan speculates, "the patient might accumulate oral envy and aggression and have in consequence bad self- and object images heavily laden with aggressive drive derivatives and experience difficulty trying to mend his aggressively and libidinally contaminated self- and object representations."

The second etiological factor Volkan mentions is "multiple mothering," where more than one mothering figure is available, complicating (through their inevitable inconsistencies) the process of integration. Finally, some persons become borderline, in Volkan's view, because of having been made the "depository of a representation of someone else as it existed in the minds of his parents" during childhood. A mother might, for example, relate to a particular child as though he or she were the reincarnation of a dead relative with whom the mother had been particularly close.

Volkan discusses in the second portion of the book a six-step program for the analytically oriented psychotherapy of borderline patients, beginning with the establishment of a reality base and progressing eventually to the mending of opposing self- and object representations that appear in the transference and finally to the development of a transference neurosis and the resolution of termination issues. These steps are illustrated by means of the case history of a young woman with whom he worked for 6½ years. At first her therapy was four times a week; later it was three times a week.

The book will appeal to readers who hold to an exclusively psychoanalytic conception of cause and treatment in the domain of borderline personality. The book will be less useful to general readers for several reasons. First, a purely psychological theory of causation, especially one that emphasizes maternal pathology, has little explanatory power. This is particularly true in the contemporary psychiatric climate, when we are beginning to recognize contributing factors of greater importance in the genesis of borderline conditions: sexual molestation, physical abuse, and constitutional risk for affective disorders, for example. Second, Volkan's formulations are not based on an adequate number of patients to permit generalization or on long-term follow-up of these patients. Third, however beneficial Volkan's therapy may have proven for Pattie, the young woman whose treatment he discusses at length, the method would seem to have little relevance to the three or four million patients with borderline personality disorder in the United States, only a tiny fraction of whom have Pattie's time and the trust fund to permit traveling a hundred miles back and forth four times a week for her therapy. Finally and most importantly, there is the question of how Volkan's approach proved efficacious. I believe Volkan helped Pattie enormously and probably also helped the other borderline patients to whom he alludes. Was their improvement mediated by Volkan's six steps, however, or by the "deep" interpretations he made? I suspect that the crucial factors were Volkan's consistency, neutrality, reliability, emphatic resonance, patience, and concern—all the human qualities that, in good therapists, exist between the lines of what they may choose to write about their patients.

MICHAEL H. STONE, M.D.  
New York, N.Y.

**The Clinical Diary of Sándor Ferenczi**, edited by Judith Dupont; translated by Michael Balint and Nicola Zarday Jackson. Cambridge, Mass., Harvard University Press, 1988, 222 pp., \$29.95.

According to psychoanalytic scholar André Haynal (1), everything Sándor Ferenczi wrote was a letter to Freud. Ferenczi became Freud's disciple in 1908, then his analysand, and then his esteemed colleague. But their lifelong friendship was ever more strained by their inherent intellectual and temperamental differences. According to Clara Thompson (2), Ferenczi's attachment to Freud was "compounded of admiration, dependence, fear of disapproval and veiled rebellion" (p. 186). On the surface, Ferenczi was an ardent psychoanalytic loyalist, but whereas Freud had little interest in or hope for the clinical applications of his work, Ferenczi was committed to them, and he had a penchant for testing an idea by pushing it to its extreme. Thus, for example, he carried Freud's concept of technical abstinence to the point of recommending extreme renunciations. When one of his patients, having given up sex and the theater, began to starve himself, Ferenczi saw the limitations of Freud's recommendations on technique.

In time, through his clinical observations and experiments Ferenczi came to a radically different position from classical theory, and he suffered for the extent to which he contradicted Freud's views. Ferenczi ultimately held that childhood neuroses were produced by parental abuse, and so he preserved the idea of pathognomonic trauma long after Freud had abandoned it in favor of infantile fantasies and drive

conflict. Ferenczi moved from the technique of extreme abstinence to the opposite pole: he allowed at least one patient regularly to kiss him at the end of each analytic session. Freud heard of this practice, and in December 1931 he wrote a critical letter to Ferenczi, calling on him to return to the psychoanalytic fold. Ferenczi instead turned to the work that is this book. The first entry in *The Clinical Diary* was written 3 weeks after Ferenczi received Freud's letter, and it affirms Haynal's impression that Ferenczi is addressing Freud, although at this time, late in his life, Ferenczi's rebellion is scarcely veiled. In the opening paragraph he states, "The so-called free-floating attention [of the analyst] amounts to no attention at all" and, he continues, makes the patient feel rejected and blamed. The analyst thereby repeats the trauma that the patient suffered at the hands of his or her parents, precluding rather than facilitating clinical improvement.

*The Clinical Diary* consists of 105 essays written in the first 10 months of 1932, when Ferenczi was losing ground in his battle against the progressive neurological implications of pernicious anemia; he died just 6 months after the last entry. There are three central and recurrent themes in the diary. First is the importance of trauma in the pathogenesis of mental disturbances of all sorts. Second is the need for the analyst to be absolutely sincere and as natural and open as possible, especially in the handling of transference issues. The analyst must always be on guard against assuming the posture of infallibility because this repeats some form of the old parental abuse. Third is Ferenczi's need to justify his differences with Freud and continue his efforts to win him over. The diary is a rich addition to psychoanalytic history, but it is also something quite else. Ferenczi's informality and insistence on freedom from lexical constraints enters into our literature a document of rare originality. Michael Balint, Ferenczi's devoted student and friend, wrote, "Ferenczi's scientific language is indeed horrifying to any purist. For Ferenczi, words . . . were only—more or less—useful means of expressing mental experience; the experience was the important thing that had to be described as strikingly as possible" (3). There is an unpolished creative spontaneity to the diary entries that reflects the expanse of Ferenczi's ranging mind. They are on love and hate, the odor of mental illness, Utopia, spirituality, the effect of curses, erotomania, and a host of other topics in addition to his late-life reflections on the therapeutic process.

This book establishes Sándor Ferenczi as the father of interpersonal psychoanalytic theory. His original ideas resurface in the works of H.S. Sullivan, D.W. Winnicott, Melanie Klein, Heinz Kohut, and Merton Gill, to name but a prominent few. His legacy has been belatedly acknowledged in a series of recent articles (4–8), in the republication of his classic paper "Confusion of Tongues Between the Adult and the Child" (9), and in André Haynal's book (1). The Freud-Ferenczi correspondence is to be published soon. *The Clinical Diary of Sándor Ferenczi* is the legacy of a brilliant man who marked with these original contributions the difficult trail of his emancipation. Perhaps the spate of recent interest in his life and work reflects the ever widening scope of psychoanalysis into interpersonal and relational issues.

## REFERENCES

1. Haynal A: *The Technique at Issue*. London, Karnac Books, 1988
2. Thompson CM: Sándor Ferenczi, MD. *Contemporary Psychoanalysis* 1988; 24:182–195
3. Balint M: Sándor Ferenczi, obit 1933. *Int J Psychoanal* 1949; 30:215–219

4. Mohacsy I, Zaslow SL, Katz C, et al: Discussions of Ferenczi's "Confusion of Tongues Between the Adult and the Child." *Contemporary Psychoanalysis* 1988; 24:207–239
5. Nemes L: Freud and Ferenczi. *Contemporary Psychoanalysis* 1988; 24:240–249
6. Dupont J: Ferenczi's madness. *Contemporary Psychoanalysis* 1988; 24:250–261
7. Lum WB: Sándor Ferenczi—the father of the empathic-interpersonal approach, part I. *J Am Acad Psychoanal* 1988; 16:131–153
8. Lum WB: Sándor Ferenczi—the father of the empathic-interpersonal approach, part II. *J Am Acad Psychoanal* 1988; 16:317–347
9. Ferenczi S: *Confusion of tongues between the adult and the child* (1932). *Contemporary Psychoanalysis* 1988; 24:196–206

JUSTIN SIMON, M.D.  
Berkeley, Calif.

**Freud in Exile: Psychoanalysis and Its Vicissitudes**, edited by Edward Timms and Naomi Segal. New Haven, Conn., Yale University Press, 1988, 310 pp., \$32.50.

It has taken a long time for the history of psychoanalysis to get beyond the level of partisan propagandizing and crude detraction. The warfare associated with ideological convictions combined with the self-interest of trade unionism still persists, but intellectual historians are now finally succeeding in incorporating studies of Freud into normal university life. *Freud in Exile* is a splendid example of the best sort of modern scholarship. It consists of revised versions of papers presented at a 1986 symposium to celebrate the opening of the Freud Museum in London; the publication was timed to coincide with the 50th anniversary of Freud's arrival in England.

Part one, the longest and most substantial part of the book, deals with the origins of psychoanalysis. Sander Gilman contributes a sophisticated article on the image of the appropriate therapist; his knowledge of Central European history is matched by his understanding of popular stereotypes and prevalent sexual beliefs. Ivar Oxaal has an interesting piece that reconsiders the Jewish background to Freud's thinking. Oxaal succeeds in elucidating the issue without exaggerating the matter through overstatement. One of the best articles is by Timms, one of the editors, who concentrates on Freud's London library and his private reading. Freud's marginal notes in the books he chose to take with him into exile in England demonstrate that his cultural interests were an essential constituent of all his creative activity. The annotations in his books establish that Freud did not read literary works, for example, for relaxation but applied a working method which reveals a considerable degree of literary sophistication.

Ritchie Robertson addresses himself to "Moses and Monotheism," the last work Freud completed. Robertson considers it Freud's "most Nietzschean book." Robertson's article deserves attention, especially because practicing analysts are apt to ignore the significance of Freud's thesis in his study of Moses. I was fascinated by all the primary documentation that Murray G. Hall comes up with in describing the fate of Freud's publishing house after the Nazis took over in Germany. Hall obviously has his finger on the pulse of old Vienna in his description of the personality of Anton Sauerwald, a chemist, the man whom the Nazis placed in charge of liquidating Freud's business affairs: "Politically speaking, he seems to have been a typical Austrian, keeping all his options open. While wearing the membership pin of the Fatherland

on one lapel, he had the swastika on the other." Hall knows that this need not mean that Sauerwald does not deserve full credit for helping to shield the Freuds from the Nazis, and he quotes the full text of Anna Freud's 1947 letter in Sauerwald's behalf.

Part two of *Freud in Exile* is titled Reception and Exile and also contains work of considerable interest. R. Andrew Paskaukas, who is editing for publication the full correspondence between Freud and Ernest Jones, has an article about their letters that contains nuggets of important quotations. Pearl King writes about the early divergences between the psychoanalytic societies in London and Vienna. Stephen Bann has an essay on the aesthetics of the Kleinian Adrian Stokes. Not all the articles are equally successful, however, and on rare occasions some authors exhibit the kind of sectarian fanaticism that has hobbled this field of inquiry in the past.

Part three, Problems of Translation, contains articles by Malcolm Pines, Riccardo Steiner, Darius Gray Ornston, Jr., Alex Holder, and Helmut Junker. Each of these works has something to recommend it, since every act of translation is also an interpretation, but I would like to raise a point that has hitherto, I think, gone undiscussed. To what extent does this concern with issues of translation tend to reinforce rather than challenge fundamentalist sorts of thinking? If we start putting our scholarly resources into refining and correcting James Strachey's standard edition of Freud's works, will there not be a tendency to slight the issue of the legitimate reservations that ought to be entertained about the substance of Freud's ideas? The new effort to mount a return to the "true" Freud is bound, I suspect, to neglect the fair-minded criticisms of his concepts that ought to be considered.

Part four, Perspectives for the Future, is the slightest of the sections, but each of the papers repays scrutiny: Earnest Gellner on the anthropological perspective, John Bowlby on changing theories of childhood, Naomi Segal on the question of women, Teresa Brennan on the feminist debate, and Walter Toman on Freud's influence on other forms of psychotherapy. I especially admired the closing piece by David Newlands, the first curator of the Freud Museum in London, which is an account of his labors at 20 Maresfield Gardens.

The editors, both dons at the University of Cambridge, deserve to be congratulated for their fine work.

PAUL ROAZEN, PH.D.  
Toronto, Ontario, Canada

**The Politics of Psychoanalysis: An Introduction to Freudian and Post-Freudian Theory**, by Stephen Frosh. New Haven, Conn., Yale University Press, 1987, 290 pp., \$30.00.

This book touches briefly on Marxism and democracy, but the real meat is in the review of psychoanalysis and its various outgrowths. In his introduction the author says, "In this book the focus is on those major traditions that most clearly bring out the differing aspects of psychoanalytic theory, especially as it relates to social thought."

Psychoanalysis is a powerful field of thought that has influenced people the world over. One has only to remember Alexander Graham Bell with his primitive telephone or Thomas Edison and his light bulb to see that basic ideas are still valid even though many changes and improvements have taken place. Freud must be viewed at least in part as a product of his time. He was not the first to realize the existence of an unconscious portion of the mind, but he was the first to

struggle with problems never before put into a cohesive theory. It is no surprise that some rejected his theory, some joined him, and some departed to pursue their own theories. It remains that Freud began the movement and that among analytically oriented workers many of his fundamental ideas remain, although modified by many, including himself. Something certainly must account for the existence of the International Psychoanalytic Association and its various members, including the American Psychoanalytic Association.

To the displeasure of many, Freud said that infants and babies are filled with sexual and aggressive instincts. It became obvious that if these instincts continued to be expressed, especially in excess, they would cause untold chaos in the world culture. External and internal forces (repression, for example) keep this from happening. In other words, the pure pleasure principle must be contained. As Freud told a mythical patient early in his career, "No doubt fate would find it easier to rid you of your illness, but you will be able to convince yourself that much will be gained if we succeed in transforming your hysterical misery into commonplace misery."

From Freud's earliest focus on the id, which is totally unconscious, analysis gradually increased its interest in the ego, only a part of which is unconscious, especially the mechanisms of defense. Frosh, obviously knowledgeable and well read, describes the movement of analysis to a larger focus. He presents both positive and negative aspects of the writings of Anna Freud, Hartman, and Erikson.

In the chapter, "Splitting of the Mind," Frosh says that Melanie Klein's particular contributions to the debates on psychological structure and development derive from the extraordinary manner in which she used concepts from both "biological" and "relationship" approaches. Frosh gives considerable attention to her ideas even though they have really never caught on in the United States. In the same chapter he explains Lacan's theories, although they also have not caused big waves in this country.

In chapter six, "Psychoanalysis and Politics," the author discusses Libertarian Freudism, paying particular attention to the writings of Wilhelm Reich, whose contributions were brilliant until his mental problems developed, and "feminist psychoanalysis." We have taken a long step from Freud's early pronouncements about the superiority of men over women and about women as castrated and inferior. Along the way progress has been made, even though some of our colleagues today look on women as relatively helpless. Too much patriarchal thought remains today but is slowly being eroded. For centuries women have been considered inferior to men in almost every sphere. It is not unexpected that great effort is needed to modify such a longstanding view, and it must be said that Frosh presents some excellent arguments in favor of the differences in psychological development of men and women.

In the chapter "Therapy and Cure" the author writes, "Psychoanalytic therapy aims at helping the individual so that he can continue to function as part of a sick civilization without surrendering to it altogether." Freud wished that psychoanalysis would avoid the use of medicine as its model. He had a premonition that psychoanalysis would become reduced to psychotherapy, eventually to be found listed under "treatments" in psychiatric textbooks.

In the chapter entitled "The Power of the Analyst" there is an interesting discussion of transference and interpretation as well as countertransference. Frosh comments, "Where classical analysts concentrate on uncovering defenses, on ego analysis, Klein's is very much an 'id psychology' dealing di-



rectly with primitive unconscious emotions of the patient's unconscious world." There follows an interesting discussion of the goal of therapy with schizoid patients, which is radically different from conventional analytic work.

In conclusion, this is a well-written book by a knowledgeable author. It covers a wide range of psychoanalytic principles and offshoots and variations of each of the theories. It should be a valuable book for any mental health worker interested in analytic principles. I highly recommend it.

STUART M. FINCH, M.D.  
Green Valley, Ariz.

**Progress in Self Psychology, vol. 3: Frontiers in Self Psychology**, edited by Arnold Goldberg. Hillsdale, N.J., Analytic Press, 1988, 287 pp., \$29.95.

Heinz Kohut's work began with strictly psychoanalytic contributions to the treatment of individuals suffering from narcissistic personality disturbances. He drew attention to cohesion of the personality, fragmentation of self-experience, and anticipatory anxiety about the occurrence of those fragmented states (fragmentation anxiety), all of which necessitated the patient's reliance on relationships with "selfobjects" for the purpose of maximizing personality cohesion. The enduring need for "selfobjects" was felt to constitute a specific fixation and showed up in specific types of narcissistic transferences: mirroring, idealizing, and twinship transferences.

In the almost 20 years since the publication of *The Analysis of the Self* (1), a large self psychology movement has arisen that has led to controversy both in and out of psychoanalytic circles. Kohut's major insights have touched off the emergence of a general self psychological approach to psychoanalysis and psychotherapy that has been hailed by some as a new science of intersubjectivity and reviled by others as a simplistic retreat from the discipline and problems inherent in doing psychoanalysis and psychotherapy. The critics feel that self psychology avoids negative transference and the distasteful regressions to infantile sexuality and primitive aggressivity, thereby depriving the patient once more of a chance to overcome his or her basic difficulties. The last two decades have seen the development of a new terminology—a clinical language of self psychology—and a core of recognized clinician-theorists who are its spokespersons. The concept of incohesiveness of self-experience has expanded to become a general aspect of the self and its need for others rather than a pathological fixation. Likewise, the concept of "selfobject" has expanded beyond a manifestation of a specific kind of pathological transference to a general aspect of human relatedness.

The literature on self psychology has tended to be quite heavily represented by reports of second analyses and therapies that correct the bunglings and insensitivities of the first therapist or analyst (who is usually mainstream or "classical"). In my opinion, the overall quality of the self psychology literature has been somewhat marred by this polemical, anticlassical agenda.

*Frontiers in Self Psychology*, volume 3 of the annual *Progress in Self Psychology* series, is by and large a refreshing exception to this trend. The book is introduced by James L. Fossage, a notable contributor to the literature on dreams. The 13 contributions are mostly outward rather than inward looking. A section on self psychology and infancy includes two strong chapters on early development and a discussion

chapter with contributions by Michael Basch, Joseph Lichtenberg, and Louis Sander. The next section deals with the psychoses. A brief introductory chapter by Arthur Malin is followed by a fascinating chapter by Robert Galatzer-Levy on the use of lithium in the experimental psychoanalytic treatment of manic-depressive patients. This chapter represents a type of integrative work that, lamentably, is underrepresented in both the psychoanalytic and the pharmacological literature. Robert Stolorow and his colleagues, George Atwood and Bernard Brandchaft, contribute an important chapter on concretization in psychotic states. In the final chapter in this section Michael Basch and Paul Tolpin discuss the preceding two chapters. The third section contains three clinical contributions. Noteworthy in this section—but not nearly detailed enough—is James Fossage's chapter "Dream Interpretation Revisited." The final section, on theoretical contributions, contains an excellent paper, "On Boundary Formation" by Russell Meares, and a fascinating, highly speculative chapter on the biological foundations of self psychology by Daniel Kriegman.

Overall, this book is worthy of its title. These are indeed, for better or for worse, the frontiers in self psychology. The editor is to be commended for his transcending the inbred and somewhat stale format that has characterized other edited volumes on self psychology. The reader interested in self psychology will be exposed to the frontiers of the movement. The more scholarly reader will be left a bit unsatisfied with the absence of in-depth considerations of major issues posed by Kohut's discoveries. For example, there is a tendency to discuss lack of personality cohesion and fragmentation as though it were perfectly clear what kinds of phenomena these are. There is also a total lack of attention to the clinical and developmental aspects of the self-conscious emotions, especially shame and envy. Finally, other than Fossage's useful chapter, there is not enough on the workings of the unconscious in dreams and fantasies. Despite these shortcomings, the book can be recommended to provide an up-to-date, useful, and largely well-balanced perspective on the state of self psychological thinking and practice.

#### REFERENCE

1. Kohut H: *The Analysis of the Self: A Systematic Approach to the Psychoanalytic Treatment of Narcissistic Personality Disorders*. New York, International Universities Press, 1971

MELVIN R. LANSKY, M.D.  
Los Angeles, Calif.

**Pragmatism's Freud: The Moral Disposition of Psychoanalysis**, edited by Joseph H. Smith, M.D., and William Kerrigan, Ph.D. Baltimore, Johns Hopkins University Press, 1986, 173 pp., \$24.50.

As this volume shows, philosophers and other humanists have much to say about the way professionals and the laity think in the post-Freudian world. Ironically, the founder of psychoanalysis tried to stem his own powerful philosophical leanings in hopes of making his science less vulnerable. These eight rather disparate essays address, in part, Freud's struggle—not least with his own ambition—and, more broadly, twentieth-century culture's efforts to assimilate, reject, or transform Freud's work.

Philosopher Richard Rorty keynotes the book with "Freud and Moral Reflection." He lives up to the editors' description

as a clear, direct, independent polemicist with a sparkling style. Noting David Hume as Freud's forebear, Rorty points to the disappearance of the human center (the soul or will) with the progressive mechanization of the psyche. He finds consolation in the dignity Freud accords our unconscious selves: "not dumb, sullen lurching brutes, but rather the intellectual peers of our conscious selves, possible conversational partners for those selves." He argues further,

Freud gave us a new technique for achieving a genuinely stable character: the technique of lending a sympathetic ear to our own tendencies to instability, by treating them as alternative ways of making sense of the past, ways that have as good a claim on our attention as do the familiar beliefs and desires that are available to introspection. His mechanistic view of the self gave us a vocabulary that lets us describe all the various parts of the soul, conscious and unconscious alike, in homogeneous terms: as equally plausible candidates for "the true self." . . . Freud has no contribution to make to social theory. His domain is the portion of morality that cannot be identified with "culture"; it is the private life, the search for a character . . . . Not until Freud did we get a usable way of thinking of ourselves as machines to be tinkered with, a self-image that enabled us to weave terms describing psychic mechanisms into our strategies of character-formation . . . . [Freud's major legacy is] the intellectual's ability to treat vocabularies as tools rather than mirrors.

Quoting Rorty is like quoting Brahms: you can identify themes, but their interconnections and harmonies are essential to appreciate the work. Self-definition and self-creation figure explicitly in this model, and I wish Rorty and those contributors concerned with immortality and will had indicated an acquaintance with the relevant work of Otto Rank, particularly *Art and Artist* (1).

In his response, Richard King brings Rorty into the orbit of Jacques Derrida and takes issue with, among others, the comment on social theory. James Earl contributes an essay on tragedy entitled "Identification and Catharsis," which veers away from Rorty, as do most of the others. David Damrosch presents a major study of Freud's ambivalent tie to Rome and its relation to his personal ambition, an essential new text for historians of psychoanalysis. Like William Kerrigan's reconsideration of Freud's memory disturbance on the Acropolis, the paper stands on its own. So does Gordon Braden's long discourse on Petrarch, "Love and Fame," which is the one chapter I found too esoteric for this collection. By contrast, "The Moral Perils of Intimacy" by philosopher Annette Baier should attract readers who usually find these topics intellectual and cold. Decrying the avoidance of love in modern moral philosophy, she writes,

It is as if our great moral theorists, since Hobbes, have tried to formulate a morality acceptable to unloving and unloved persons, an impersonal morality . . . . The moral heritage of our patriarchal past includes not only the myth of the paternal omniscient authority but also that of the loving father. Moralities that require of us that we love, and respond to love, can be equally apt to encourage tyranny and coercion . . . . Motherlove . . . has to avoid both exploitation of the mother's immensely superior power and that total self-abnegation that turns the infant into the tyrant. Love between unequals in power is good of its kind when it prepares the

less powerful one for love between equals . . . . We urgently need a new assignment of social roles, and a new morality [to guide us] on how to treat those close to us so that closeness, chosen or not chosen, can be sustained without domination or mutual suffocation, as well as on how to respect the rights of strangers so that distance does not entail moral neglect. (p. 100)

Not surprisingly, Baier cites social scientists Carol Gilligan and Nancy Chodorow in her call for a moral theory that makes sense to lovers as well as to strategists, religionists, and statisticians.

Although it is a bit of a hodgepodge, this volume will outlast most books that psychiatrists encounter in a year or two. As a philosophical amateur, I am glad to have read it and to have it on my shelf.

#### REFERENCE

1. Rank O: *Art and Artist* (1932). New York, WW Norton, 1989

E. JAMES LIEBERMAN, M.D.  
Washington, D.C.

#### CLINICAL ASSESSMENT

**International Classification in Psychiatry: Unity and Diversity**, edited by Juan E. Mezzich, M.D., Ph.D., and Michael von Cranach, M.D. New York, Cambridge University Press, 1988, 390 pp., \$59.50.

Perhaps the one thing that all psychiatrists have in common is their basic medical training. Wherever that took place, it is likely that its content differed from one medical school to another only in detail, and it is virtually certain that all of us were taught the necessity for thorough assessment, differential diagnosis, and diagnosis. The content of our psychiatric training, however, could differ enormously according to the era of training, the geographic location in which it occurred, and the theoretical background of each particular school. We know that in some schools there was a bias against systematic diagnostic procedures, and in retrospect this can be seen to have been a deadly error.

In the past generation, psychiatry has become a therapeutically active and, in many ways, a therapeutically more optimistic specialty. To be specific, however, treatments have to be related to verifiable diagnoses, and we are only beginning to edge toward that situation. New technologies will undoubtedly make enormous advances in linking specific illness with specific treatment in the coming decades. We should be honing our clinical skills in preparation.

DSM-III was not perfect, but North American psychiatry owes it an enormous debt of gratitude for firmly reemphasizing the central preliminary role of classification and diagnosis in rational treatment. It also insisted on an atheoretical approach to diagnosis, which some authorities dislike because they find it difficult to separate etiological speculation from syndrome description. Despite its shortcomings, DSM-III adopted a less parochial, more international approach, and it is fascinating to see that many other nationalities have responded positively to it and to its modification, DSM-III-R. I have visited a number of countries in recent years in various parts of the world where DSM-III and DSM-III-R are being accepted as standard diagnostic guidelines. I can

even report that some of my former senior British colleagues are beginning to take *DSM-III* very seriously. There can be no greater compliment than this.

The title of this book, *International Classification in Psychiatry: Unity and Diversity*, almost says it all. This is a collection of papers from the World Psychiatric Association Conference on Classification in Psychiatry, held in Montreal in 1985. It ranges across international and certain national diagnostic systems, looks at specific syndromes, considers terminology and important nosological issues, and discusses aspects of assessment instruments. It ends with a (disappointing) panel discussion on the forthcoming *ICD-10*, but it is really *DSM-III* that sneaks away with the honors throughout the book. The impact of *DSM-III* on a worldwide professional audience has clearly been profound, and one really begins to feel that an international system of language and knowledge in psychiatry is standing on the threshold.

This book is essentially a collection of short essays, including a small number of investigative reports. It adds little that is new to our sum of knowledge, and, in fact, it is a little out-of-date because *DSM-III-R* emerged after the conference. However, *ICD-10* is not yet out and is awaited with considerable interest because it is likely to converge with *DSM-III-R* in some important areas, so the book can be read with profit as a lead-up to the appearance of the new World Health Organization classification.

The main interest for me in this volume was the underlining of traditional differences in case assessment and diagnosis in different countries. The chapters on French classification by Pull, Pull, and Pichot and Scandinavian classification by Strömberg are especially revealing about how we can all observe the same phenomena yet interpret them very differently as a result of preconceived philosophies, theoretical frameworks, and semantic idiosyncrasies. The good news is that there seems to be increasing willingness today to cross the boundaries of language and culture and to see more and more the huge similarities in particular mental disorders, in whatever country they occur.

This is not an enthralling book, but it is a salutary one. I recommend it to psychiatrists of every stripe as a reminder that good diagnosis is the keystone of any medical approach, and psychiatry can be no exception. However, there is one element that the book hardly touches on, and which I think we should all grasp: that is, the increasing speed of change in our knowledge base. *DSM-III-R* is hardly out and already the process of preparing *DSM-IV* has begun. *ICD-10* will be outdated before it is published, and no doubt *ICD-11* will have to be considered before long. It is frightening but exhilarating and undoubtedly means that our specialty is on the move. Stringent diagnostic habits will be among the factors that will help keep it on the right lines.

ALISTAIR MUNRO, M.D.  
Halifax, Nova Scotia, Canada

**Clinical Assessment of Malingering and Deception**, edited by Richard Rogers. New York, Guilford Press, 1988, 365 pp., \$39.50.

Not many readers would argue with the proposition that all of us have lied and all of us have been lied to. With the human capacity to deceive known to us firsthand, our curiosity about those who dissimulate comes easily. In the clinical setting, malingering and deception may be important subtexts, and they are very often explicit themes in forensic

and disability examinations. The need for more information in this area can be satisfied through this informative volume.

The editor has assembled a book that covers the full spectrum of psychiatric and medical deception, including diagnostic issues, psychometric and other methods of detection, and research issues. The breadth of coverage is especially good. The authors are very candid about the limitations of detection methods, which are substantial enough to be disheartening to the clinician. They are also sensitive to many of the ethical dilemmas involved in clinical applications and research methods in this field. There are penetrating discussions and critiques of the research methods that detection of deception is based on.

The opening chapter defines the terms used in the book, and this is very helpful. Malingering is defined in accordance with *DSM-III* as conscious fabrication. Defensiveness is used as the opposite of malingering—that is, the conscious denial or minimization of symptoms. The subsequent chapters discuss medical and psychiatric syndromes associated with the various forms of deception. These are generally useful and clearly presented, although there are occasional, grating redundancies. Important unifying features applied throughout the book are tables listing two sets of criteria for each type of deception: 1) threshold criteria that would lead the clinician to suspect the presence of a given disorder and 2) criteria that would fulfill requirements for a disorder.

Material on malingered posttraumatic stress disorder (PTSD) is well done. However, the chapter on PTSD also includes material on other disorders that appear after injury. By using the term "posttrauma" rather than the more precise term "postinjury" when referring to syndromes occurring after injury, the author is less clear than he might have been. Nonetheless, there is still a lot that is useful in this chapter, including a discussion of so-called compensation neurosis.

An excellent chapter on children and deception discusses moral development, including the work of Piaget and Kohlberg as well as more recent research. Of particular value is a clear and concise discussion of the assessment of deception in children. This is a troublesome area laden with risk because decisions are made in cases involving accusations of sexual abuse, child custody cases, and other matters that have immense repercussions.

The chapters on psychometric approaches to detecting deception tend toward the technical and are probably of greatest interest to those who administer such tests. Of importance to all of us is the clear conclusion that deficits can be faked on almost any existing test. Of some small solace is the observation that symptoms cannot be minimized on neuropsychological and intellectual testing—that is, one cannot appear better than one really is. The chapter on neuropsychological measures is extremely clear and the most instructive in this section of the book, elaborating principles that have broad applicability.

In some ways, the chapter on polygraph techniques is chilling. The imprecision of the technique, the necessity of using deception to detect deception, and the tendency for errors to favor false accusation of the innocent are all worth knowing about. The authors of this chapter as well as other chapters on special techniques are very clear about the frail nature of much of the research forming the basis of these techniques. At the same time, there are interesting discussions of how research should be done and on newer experiments in detection of deception. Chapters on hypnosis, structured interviews, and evaluation and research involving sex offenders, including the use of phallometric techniques, are included.

The final two summary chapters on clinical methods and



research are indeed clear summaries. I would suggest that, after reading the introduction and skimming the section on diagnostic issues, the reader turn to the summary chapters before plunging into a more detailed reading of the entire book.

We are cautioned to suspect deception in our clinical work. Although this is good advice, it is unnerving. Having to consider that our patients might be lying to us rather than manifesting symptomatic behavior has the potential for distorting the therapeutic relationship. On the other hand, it gives one pause when patients do such things as commit suicide in an obviously carefully thought out manner after denying such intent or deliberately minimize symptoms in order to be accepted into therapy.

If one believes that detecting deception is an easy matter, this book will lay that concept to rest. Dissimulation is an important human behavior. Deceptive behavior has myriad origins and manifestations, making it no wonder that its detection is difficult. This is a forthright and useful book for those interested in learning more about this phenomenon.

ARNOLD WERNER, M.D.  
*East Lansing, Mich.*

## PSYCHOSOMATIC DISORDERS

*Psychosomatic Disorders*, by Benjamin B. Wolman. New York, Plenum, 1988, 312 pp., \$39.50.

The author refers to this volume as "an encyclopedic book on psychosomatic disorders . . . It covers the entire field of mind-body issues in psychology and psychiatry and related areas of clinical medicine." It is directed to advanced students in medicine and allied professions. Neither an alphabetical-order encyclopedia nor a multiauthored compendium but a compact, concise, and easily readable digest, this volume is remarkably successful in its stated aim. It is organized into four major parts: Foundations, Etiological Considerations, The Disorders, and Treatment Methods. Each chapter is subdivided into a total of more than 200 topical headings. The extensive references are placed at the ends of chapters. There are organizational difficulties and some awkwardness of topic flow and repetitiveness, but this multidimensional discipline is not easily organized into a straight-line narrative.

The book begins with the ancient dualism controversy (psychosomatics being the intersection of medicine with philosophy); the author acknowledges the lack of resolution of the mind-body debate. Each unquestionably influences the other, and psychosomatic medicine is concerned with the capacity of the mental system to produce physical illness. Admittedly, how psychological or social experiences are transduced into pathogenic physiology remains obscure.

After the historical overview, Wolman covers psychoanalysis, neurophysiology, and the immune system as foundations of theory. As etiological factors he discusses stress, conditioning, society and culture, family relations, and personality. The sections on the disorders and treatment methods include the topics one would wish to see, including psychosomatic issues in the "purely" mental disorders of anxiety, school phobia, conversion hysteria, depression (with

mania), and schizophrenia. The emphasis here is on the physical symptoms accompanying these primarily mental disorders. In closing, the author emphasizes comprehensive and flexible treatment, considering the behavioral, affective, cognitive, interpersonal, and biological components of the human mental system.

As a counterpoint to the excellent scholarly review, another voice makes a periodic appearance: the author presents theories and conclusions from his own work, views that many readers may find debatable. Regarding the monism-dualism debate, Wolman favors "monistic transitionism" as a resolution. According to this theory, matter evolves in three phases: inanimate, organic, and psychological:

At a certain phase in evolution, matter turns into psychological processes (which can also be called behavioral). Transitionism links all three phases into one process of continuity. This process is also reversible, for, as the inorganic matter may become organic matter, and the organic matter may become psychological, the psychological elements can turn organic and organic elements can turn inorganic. (p. 48)

This is a provocative idea; sort of a psychological  $E=MC^2$ . However, the lengthy argument presented as its logical foundation is unconvincing.

Wolman also states unequivocally that "psychosomatic symptoms always carry a message. All of them serve the same purpose: escape from a difficult, embarrassing or painful situation" (p. 48), a theme reiterated throughout the book. Although he cites Alexander's statement that the viscera are incapable of expressing ideas because of their autonomic control, he rejects it in his interpretation of psychosomatic processes. In taking this narrow position, Wolman overlooks the important distinctions among such somatizing disorders as conversion disorder, hypochondriasis, malingering, and factitious disorders clearly presented by Ford (1).

The concept of stress is oversimplified to an unmitigated evil force. Stress is "a reaction of the organism to noxious or threatening stimuli," coming mostly "from without, from one's physical or social environment." Although physicians deal with stressful environments in wartime (Dr. Wolman was a military psychiatrist in World War II), the most frequent source of psychosomatic disorder in the affluent peacetime United States is the inability to achieve closure on fantasized fears and aspirations, not the effects of bombs or famine. A heuristically more productive concept acknowledges stress as a reaction that under certain physiological conditions (exercise and study) produces strength and growth but becomes pathogenic under conditions of excesses. Exploration into the autonomic responses in chronic decompensation will help clarify disease formation.

It would be useful to include the work of Edmund Jacobson (2), who coined the term "progressive relaxation" and laid the foundation of the study of the motor system in relationship to thought, impulse, and behavior on one hand and the autonomic reactions on the other. Study in this area can help unravel the transduction problem.

This little volume is densely packed with fine scholarship. It is a brief, intensive walk through a large field. Unfortunately, I feel it is compromised, especially for textbook purposes, by the author's not exercising the same academic restraint on his own ideas as he did on those of others.

## REFERENCES

1. Ford CV: *The Somatizing Disorders*. New York, Elsevier, 1983
2. Jacobson E: *Progressive Relaxation*. Chicago, University of Chicago Press, 1929

ARNOLD H. GESSEL, M.D.  
Rose Valley, Pa.

## PSYCHOLOGICAL TESTING

**Psychological Testing From Early Childhood Through Adolescence: A Developmental and Psychodynamic Approach**, by Miriam G. Siegel. Madison, Conn., International Universities Press, 1987, 529 pp., \$50.00.

Dr. Siegel, in both her title and her preface, promises that this book will be broad, coherent, and accessible. The work, she says,

is addressed to psychologists, psychiatrists, social workers, educators, and other members of the helping professions who deal with children and adolescents . . . It concentrates on several time-honored instruments that have established their practical usefulness and are widely used in psychodiagnostic work with children. The book is written from developmental and psychodynamic perspectives, and its approach is holistic. Its central purpose is to delineate a method of test analysis that evokes a picture of a singular child. (p. vii)

This advance billing piqued my interest in becoming clearer about theoretical foundations and empirical applications of some of the best-known psychological tests for assessing child and adolescent development.

These promises are only partly fulfilled. On the positive side, readers will find many important strengths. They will discover a highly experienced psychologist who is committed to a very specific perspective but not controlled by it. Throughout the book Dr. Siegel offers strong arguments, by proclamation and example, of the importance of using multiple strands of evidence—tests, interviews, and direct observation—to capture the many-sided nature of a child or adolescent's development and personality. She frequently shows us excellent examples of the way that observation, history, and test data can be integrated to give a diagnostic picture and predictions about clinical course. We find many instances of a skilled practitioner at work. Dr. Siegel vividly conveys test behaviors and impressions, smoothly moving from quantitative description of test results to intriguing speculations about the meaning of results obtained from projective tests.

Part one, *The Psychological Examination*, presents basic aspects of examining a child through a variety of instruments and, most importantly, offers thoughtful discussions about the nature of these instruments. Among the instruments covered are the Wechsler Intelligence, Rorschach, Thematic Apperception, Human Figure Drawing, and Bender-Gestalt tests. I was especially pleased by the excellent chapter on the nature of projective tests entitled "Projective Techniques: Theory and Overview."

In part two there is a series of long case studies (with many observations and test protocols) ranging from a 3-year-old child ("Charlie") to several children in their late adolescence. It is in these case studies that Dr. Siegel most intimately

reveals how she proceeds to test, think about her data, integrate observations, and communicate with clinicians and (sometimes) with parents. Also helpful are the brief follow-up vignettes that she provides at the end of each of the case histories.

With all of the strengths, one might wonder, why did I feel my high hopes dashed by this book? There are difficulties that dampened my otherwise enthusiastic response. First, although Dr. Siegel notes that her framework is psychodynamic and developmental, in the end I felt that the very heavy psychodynamic scaffolding interfered with an openness to other theoretical perspectives for understanding development. There are many references to psychoanalytic constructs such as superego, ego, and defenses. Although I have no problem with an explicit commitment to a theoretical approach, I think that social cognition, general cognition, and at times neuropsychological perspectives could have been helpful in alerting the reader to complexities of development and its assessment.

A second difficulty has to do with the lack of integration between the two parts of the book. Cases are introduced in the second part, following the introduction of each test. However, even though I have some knowledge of these tests, I found it necessary frequently to flip back to some of the original chapters to make sense of the statements and conclusions in the later chapters. Although some of this to-and-fro activity in reading such a book may be inevitable, I think that it might have been diminished by introducing threads of the various cases within the conceptual material, anticipating some connections to these later case reports.

The third difficulty that makes appreciation of the case material difficult is the level of explanation about the test variables. Although the Bender-Gestalt and the Thematic Apperception tests and data are presented and explained very thoroughly, this is not the case for the Rorschach data. A relatively brief chapter in the first part of the book only partially prepared me for the Rorschach data. The stimuli for each Rorschach card are not well described. When the responses to the cards and the inquiries within the cases are presented, it is very hard to understand what the actual stimuli were. Surely it could have been possible to provide, at the very least, photographs of each of the Rorschach cards in either the earlier chapters or later. Creating even further difficulties with understanding these Rorschach protocols are the many scores given: W, F, H, FM. Some of these variables are explained in the Rorschach chapter, but not to the extent needed to understand the meaning of these many symbols and notations in the later part of the book. Although this technical language may be understandable to the experienced psychological tester, it is not obviously accessible to the more generally curious reader, such as myself, or to the others for whom this book is addressed. My difficulty with this aspect of the book was especially heightened when quantitative data were given regarding locations, determinants, and various ratios of the symbols. I think it is fine to present such detailed data, but it is then incumbent on the author to provide an explanation of what these data mean. Finally, I was startled by the book's sudden ending with the last case history, "Henrietta: Adolescent Anorexia." A concluding section summarizing some of the themes and issues raised by the cases, developing questions for future research, or pulling together many of the clinical and conceptual issues would have been useful in providing some synthetic overview of the multistranded data and speculations offered by the author.

Despite these various misgivings, I would still recommend this book to practitioners and psychological researchers who

want to gain an appreciation of the subtleties of clinical psychological testing. This book provides a fine glimpse of the workings of the mind and the practice of a skilled and thoughtful psychologist. As such, it may whet the appetite of those of us who would like to gain more understanding about this very special kind of clinical-developmental psychological assessment. The diversity of data presented and the subtlety of psychological responses to the life cycle described by Dr. Siegel enhance our appreciation of the many tools that can be used to grasp facets of how boys and girls pursue normal and pathological developmental paths.

STUART T. HAUSER, M.D., PH.D.  
Boston, Mass.

**Primitive Mental States and the Rorschach**, edited by Howard D. Lerner and Paul M. Lerner. Madison, Conn., International Universities Press, 1988, 635 pp., \$65.00.

There can be little doubt that, after its predicted demise in the late 1960s and early 1970s, the field of personality assessment has refuted critics and doomsayers alike and undergone a powerful resurgence. This growth is evident in the amount and quality of published research, the recent inauguration of a major new journal devoted entirely to psychological assessment (*Psychological Assessment: The Journal of Consulting and Clinical Psychology*), and the popularity of professional conferences and workshops with personality assessment as their primary focus.

Developed in the second decade of this century by the brilliant Swiss psychiatrist Hermann Rorschach, the inkblot test has been at the center of this resurgence. It has been aggressively attacked by academic psychologists for its lack of scientific validity and by humanistic psychologists for its pathologizing focus, but it has remained a widely used and clinically useful tool. Largely through the empirical work of Dr. John Exner (1-3) and assisted by the continued growth and productivity of the psychoanalytic school of interpretation, the Rorschach has found a new respectability and has acquired a new generation of enthusiastic adherents. It is now more popular and solidly grounded, both empirically and conceptually, than ever before.

*Primitive Mental States and the Rorschach* follows and complements an earlier text, *Borderline Phenomena and the Rorschach Test* (4), and provides a weighty collection of research and clinical papers addressing "primitive, archaic, or preoedipal phenomena and psychopathology." Written primarily from a psychoanalytic perspective, these papers focus on depression, suicidality, incest, sexual perversion, eating disorders, and transsexualism as well as the old standards—borderline, narcissistic, and schizophrenic disorders. The four psychologies of psychoanalysis (5) are represented here, with a special emphasis on object relations theory.

This is not a text for everyone. Given its highly technical and often esoteric focus, the book is most likely to appeal to Rorschach specialists. The enduring strength of the inkblot test, and a particular merit of this volume, is concern with understanding inner experience as revealed by what is seen in the blots. This is fundamentally a humanistic concern and assumes dramatic new meaning as psychiatry, in its endeavor to remedialize, becomes focused more and more on brain amines and neuroanatomy and less and less on personal meaning and significance. Despite the technical and arcane science that has grown up around it, the Rorschach remains a window into the psyche.

*Primitive Mental States and the Rorschach* demonstrates both the strengths and limitations of contemporary psychoanalytic interpretation in Rorschach testing. Like previous Rorschach texts, it reveals the richness and as yet untapped genius of Rorschach's test.

#### REFERENCES

1. Exner JE: The Rorschach: A Comprehensive System, vol 1: Basic Foundation, 2nd ed. New York, John Wiley & Sons, 1986
2. Exner JE: The Rorschach: A Comprehensive System, vol 2: Current Research and Advanced Interpretations. New York, John Wiley & Sons, 1978
3. Exner JE, Weiner IB: The Rorschach: A Comprehensive System, vol 3: Assessment of Children and Adolescents. New York, John Wiley & Son, 1982
4. Kwawer JS, Lerner HD, Lerner PM, et al: Borderline Phenomena and the Rorschach Test. New York, International Universities Press, 1980
5. Pine F: Developmental Theory and Clinical Process. New Haven, Yale University Press, 1985

MARVIN W. ACKLIN, PH.D.  
Honolulu, Hawaii

#### CROSS-CULTURAL PSYCHIATRY

**Clinical Guidelines in Cross-Cultural Mental Health**, edited by Lillian Comas-Díaz and Ezra E.H. Griffith. New York, John Wiley & Sons, 1988, 361 pp., \$39.95.

The progressive blossoming of cultural psychiatry over the past decade has been due in great part to the efforts of scholars who have established a sound theoretical and research base for the field. The purposes of this book are "to provide therapeutic suggestions and guidelines to the practitioner working within a cross-cultural setting" and to serve as "a resource for trainees from all the clinical disciplines" (p. xi).

The first section examines family values, language, religion, race, and political ideology as factors that greatly influence the provision of mental health care. Russell's chapter on "Language and Psychotherapy: The Influence of Non-standard English in Clinical Practice" is particularly comprehensive, insightful, and well referenced. Hickling's report on the dramatic interplay between politics and psychotherapy in Jamaica is an eye-opener. Although politics has not intruded on psychiatric practice in the United States as forcefully as it has in some other countries, one cannot help but wonder about political influences that subtly affect diagnosis and treatment.

The second section discusses clinical practice with special groups such as Afro-Americans, Puerto Ricans, Cubans, and West Indians. The chapter by Cervando Martinez on Mexican-Americans is especially sympathetic and perceptive. The chapter by Mollica and Lavelle on Southeast Asian refugees reveals the centrality of the "trauma story" in psychotherapeutic interventions with refugees.

The third section consists of a thoughtful chapter on cross-cultural mental health treatment, with suggestions for future directions in training and research.

*Clinical Guidelines in Cross-Cultural Mental Health* certainly is a worthwhile book, although each chapter could be expanded easily into a book of its own. As the editors note, it is difficult to portray the "dynamic reality" of an ethnic group whose members have differing educational back-

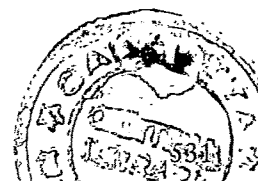


grounds, social statuses, and levels of acculturation. Thus, we are presented with a somewhat static picture that "offers us a point of departure for conceptualizing more clearly the delivery of clinical services that are culturally relevant" (p. 4). I found many of the chapters to be useful reading for

residents in my seminar on the sociocultural foundations of psychiatry.

ARMANDO R. FAVAZZA, M.D., M.P.H.  
Columbia, Mo.

*Reprints of Book Forum reviews are not available.*



## Letters to the Editor

### Serious Adverse Effects of Combining Fluoxetine and Tricyclic Antidepressants

SIR: Fluoxetine inhibits the metabolism of tricyclic antidepressants and benzodiazepines (1–3). We believe that this letter is the first to document serious adverse effects due to this phenomenon.

Mr. A, a 69-year-old white man with recurrent depressive disorder, had been treated for 2 months with desipramine, 125 mg/day (his plasma concentration reached 171 ng/ml). After he was hospitalized, his desipramine dose was tapered to 50 mg/day, and fluoxetine, 20 mg/day, was added. Although the patient initially improved, within 10 days he developed delirium: marked short-term memory impairment, confusion, agitation, constructional apraxia, mild aphasia, and impairment in calculations. His desipramine level was 390 ng/ml. Both drugs were discontinued, and over the next week Mr. A returned to his baseline state.

Ms. B, a 28-year-old white woman with panic disorder, had been treated for 5 months with imipramine, 300 mg/day (her combined imipramine/desipramine plasma concentration reached 276 ng/ml), and alprazolam, 8 mg/day. Breakthrough panic attacks led to the addition of fluoxetine, 20 mg/day. Ms. B experienced a resolution of her panic attacks and reported that fluoxetine had been "very helpful." After 10 weeks, however, she experienced a grand mal seizure. An emergency room workup produced no abnormal findings except a combined imipramine/desipramine plasma concentration of 945 ng/ml. All medications were discontinued. She has not had another seizure during 1 year of follow-up.

Ms. C, a 37-year-old white woman with bipolar disorder, type II, depressed phase, had been treated with doxepin, 300 mg/day (serum level unknown), lithium carbonate, 1200 mg/day (serum level=0.86 meq/liter), and alprazolam, 2 mg at bedtime as needed for sleep. After 3 months, fluoxetine, 20 mg/day, was added for 2 weeks and then increased to 40 mg/day coincident with a reduction in doxepin to 250 mg/day. After 2 months, Ms. C had a grand mal seizure. An emergency room workup produced no abnormal findings except a combined doxepin/desmethyl-doxepin plasma concentration of 489 ng/ml. The patient stayed on this regimen for an additional 2 weeks because of delayed reporting. When the results became known, a repeat sample revealed a combined level of 783 ng/ml. The medications were stopped.

None of these patients had had previous seizures or delirium. These cases illustrate the value of monitoring levels of tricyclic antidepressants to prevent toxicity and underscore the potential danger associated with fluoxetine-induced inhibition of metabolism. In comparison to other cases of tri-

cyclic toxicity alone (4), fluoxetine did not appear to increase the toxicity of tricyclics beyond inhibiting their metabolism. Important questions remain. In what percentage of patients will fluoxetine inhibit metabolism of tricyclics? What drugs, besides tricyclics and certain benzodiazepines, will have their metabolism inhibited by fluoxetine?

### REFERENCES

1. Lemberger L, Rowe H, Rosoworth J, et al: The effect of fluoxetine on the pharmacokinetics and psychomotor response of diazepam. *Clin Pharmacol Ther* 1988; 43:412–419
2. Vaughan A: Interaction of fluoxetine with tricyclic antidepressants (letter). *Am J Psychiatry* 1988; 145:1478
3. Aranow RB, Hudson JI, Pope HG Jr, et al: Elevated antidepressant plasma levels after addition of fluoxetine. *Am J Psychiatry* 1989; 146:911–913
4. Preskorn S, Jerkovich G: Central nervous system toxicity of tricyclic antidepressants: phenomenology, course, risk factors, and role of therapeutic drug monitoring. *J Clin Pharmacol* (in press)

SHELDON H. PRESKORN, M.D.  
JORGE H. BEBER, M.D.  
Wichita, Kan.  
JOHN C. FAUL, M.D.  
Denver, Colo.  
ROBERT M.A. HIRSCHFELD, M.D.  
Rockville, Md.

### Overcoming Hypersensitivity to Fluoxetine in a Patient With Panic Disorder

SIR: Despite growing evidence of fluoxetine's usefulness in obsessive-compulsive disorder (1) and panic disorder (2), some patients with these disorders initially have great difficulty tolerating customary doses of the drug. In one study, seven of the eight panic disorder patients who were able to tolerate 10–70 mg/day of fluoxetine achieved complete remission of their panic attacks, but eight of the total of 16 patients studied were unable to tolerate even 10 mg/day of fluoxetine (2). Panic disorder patients, in particular, are known for their hypersensitivity to a variety of medications, including psychostimulants and antidepressants. (The "jitteriness" syndrome, which occurred in 31% of antidepressant-treated panic disorder patients in one study [3], often limits compliance [4].) The following example illustrates one such response to fluoxetine and the way in which it was successfully handled.

Mr. A, a 24-year-old man, sought treatment for longstanding semisituational panic attacks, night terrors, generalized anxiety, and a tendency to worry obsessively about his health. In the past, imipramine and desipramine had provided some relief from the panic attacks and night terrors, but side effects remained troublesome, even after a year, so both medications were discontinued.

Following a single 20-mg dose of fluoxetine, Mr. A experienced 18 hours of intense and extremely uncomfortable nervousness, headache, inability to concentrate, and exacerbation of panic symptoms. Subsequent test doses confirmed his inability to tolerate 10-mg and even 5-mg doses. He was therefore instructed to dissolve the contents of one 20-mg capsule in 100 ml of water or apple juice and to begin by taking 5 ml of the solution, or 1 mg of fluoxetine, nightly. The solution was kept refrigerated; it is said by the manufacturer to have a shelf life of 14 days under these conditions (Eli Lilly and Co., Medical Department, personal communication).

Surprisingly, even with the 1-mg dose, the patient noted some jitteriness, difficulty concentrating, and increase in panic attacks, but these diminished over the next 2 weeks. Subsequently, the dose could be increased in 1-mg and then 2-mg increments approximately every 2 weeks; it reached 10 mg/night after 2½ months. Interestingly, it took 3–4 days for the effects of each increase to be fully felt; this was later found to be consistent with the accumulation kinetics of fluoxetine and its active metabolite, norfluoxetine (5).

At a dose of 10 mg/night of fluoxetine, Mr. A reported that his night terrors and panic attacks had virtually disappeared and that the generalized anxiety and obsessive worrying were greatly diminished. Two months later the gradual reemergence of obsessive worrying prompted a stepwise increase to 20 mg/night. At this writing, 3 months later, the patient continues to feel well, tolerates the medication well, and claims it has “changed [his] whole life” in a very positive way.

I understand that the manufacturer of fluoxetine may soon be marketing a stable liquid preparation which would make this titration process easier.

#### REFERENCES

1. Fontaine R, Chouinard G: An open clinical trial of fluoxetine in the treatment of obsessive-compulsive disorder. *J Clin Psychopharmacol* 1986; 6:98–101
2. Gorman J, Liebowitz MR, Fyer AJ, et al: An open trial of fluoxetine in the treatment of panic attacks. *J Clin Psychopharmacol* 1987; 7:329–332
3. Pohl R, Yeragani VK, Balon R, et al: The jitteriness syndrome in panic disorder patients treated with antidepressants. *J Clin Psychiatry* 1988; 49:100–104
4. Noyes R, Garvey MJ, Cook BL, et al: Problems with tricyclic antidepressant use in patients with panic disorder or agoraphobia: results of a naturalistic follow-up study. *J Clin Psychiatry* 1989; 50:163–168
5. Lemberger L, Bergstrom RF, Wolen RL, et al: Fluoxetine: clinical pharmacology and physiologic disposition. *J Clin Psychiatry* 1985; 46(3, section 2):14–19

MARK E. GIESECKE, M.D.  
Philadelphia, Pa.

#### Anticholinergic Side Effects of Trazodone Combined With Another Pharmacologic Agent

SIR: Trazodone, a triazolopyridine antidepressant, has been used widely in psychiatry, in part because of its apparent lack of anticholinergic side effects (1, 2). This feature is particularly helpful in treating patients with depressive disorders and concurrent physical ailments such as glaucoma,

prostatic hypertrophy, and constipation. Two reviews (3, 4) have corroborated the observation that trazodone has a very low incidence of anticholinergic side effects. However, it may not be safe to assume a complete absence of anticholinergic potential with trazodone. The following case suggests a need for caution when trazodone is used concurrently with another pharmacologic agent that has anticholinergic effects.

Ms. A, a 69-year-old white woman, presented with symptoms of depression, early morning awakening, decreased appetite, and a 10-lb weight loss during the preceding 3 months. She had been taking isopropamide iodide, an anticholinergic antispasmodic drug, for a spastic colon. Her other medications included atenolol (a  $\beta$  blocker) for hypertension, estrogen replacement, diazepam intermittently, and an occasional potassium supplement. While we were consulting with her other physicians regarding her medications, particularly the  $\beta$  blocker, we decided that a trial of an antidepressant was indicated. Ms. A was started on trazodone, 75 mg/day, because of its low anticholinergic properties. The day after taking the first tablet of trazodone, she experienced urinary retention and went to an emergency room for catheterization; she was advised to discontinue the trazodone. Two days later, the patient, on her own initiative, decided to reinstitute the trazodone; she again experienced urinary retention. After she again stopped the trazodone and consulted us, we discontinued the isopropamide iodide and restarted the trazodone. Within 2 weeks, on a regimen of 100 mg/day of trazodone, Ms. A felt less depressed and more energetic, and there was no recurrence of urinary retention. She sustained her improvement on the 100-mg/day dose.

This patient had not experienced urinary retention when taking either isopropamide iodide or trazodone alone. The urinary retention only occurred on two occasions when both agents were being used concurrently. We suspect that the additive effects of using the minimally anticholinergic trazodone with the isopropamide iodide were sufficient to bring about the episodes of urinary retention. Of course, there are alternative explanations, such as alterations in the metabolism of both drugs. We were unable to find reports of a similar drug interaction in the current literature. Clinicians should use caution in prescribing even minimally anticholinergic antidepressants simultaneously with other anticholinergic medications, particularly for older adults.

#### REFERENCES

1. Gershon S, Newton R: Lack of anticholinergic side effects with a new antidepressant—trazodone. *J Clin Psychiatry* 1980; 41:100–104
2. Taylor DP, Hyslop DK, Riblet LA: Trazodone, a new nontricyclic antidepressant without anticholinergic activity. *Biochem Pharmacol* 1980; 29:2149–2150
3. Rakel RE: The side-effect profile of trazodone, in Desyrel (Trazodone HCl), A Compendium of Three Years of Clinical Use: Proceedings of a Symposium, Sept 14, 1984. Evansville, Ind, Mead Johnson Pharmaceutical Division, 1984
4. Robinson DS: Adverse reactions, toxicities, and drug interactions of newer antidepressants: anticholinergic, sedative, and other side effects. *Psychopharmacol Bull* 1984; 20:280–290

CARLYLE H. CHAN, M.D.  
ROBERT J. RUSKIEWICZ, M.D.  
Milwaukee, Wis.



## MAOIs and Ménière's Syndrome

SIR: This letter reports a case in which there was an apparent association of Ménière's syndrome with monoamine oxidase inhibitors (MAOIs). This association is not mentioned in the *Physicians' Desk Reference*. Parke-Davis has had no previous reports of it with phenelzine, though tinnitus alone has been reported with tricyclic antidepressants (1).

Ms. A, a 41-year-old depressed woman, was an alcoholic who had been sober for 2 years; she had responded to ECT but not to tricyclic antidepressants. She was in generally good physical health, but she had a history of periodic edema in her legs, for which she took diuretics as needed, although no diagnosis had been established. There was no personal or family history of Ménière's syndrome.

The first MAOI Ms. A received was phenelzine, to which she responded at a dose of 90 mg/day, but which caused edema in her extremities and weight gain (16 lb)—side effects that are reported in the *Physicians' Desk Reference*. Four weeks after beginning to take phenelzine, she developed typical symptoms of Ménière's syndrome, with true vertigo and tinnitus. An ear, nose, and throat specialist tried meclizine and subsequently performed surgery, inserting a shunt, because of the severity and frequency of the attacks. However, when phenelzine was restarted after the surgery, Ms. A again developed edema in her extremities and symptoms of Ménière's disease, although they were not as severe as previously.

The phenelzine was discontinued, and the patient was given a trial of tranylcypromine, up to 60 mg/day, but 6 weeks later she had another episode of Ménière's syndrome. She then tried bupropion and experienced neither benefit nor Ménière's symptoms. Next, she was given isocarboxazid, up to 30 mg/day, but developed Ménière's symptoms 5 weeks later. She then tried fluoxetine, which also produced neither benefit nor side effects. Finally, she received pargyline, up to 50 mg/day, and had an attack of Ménière's syndrome 3 weeks later. Thus, a pattern had emerged: each MAOI resulted in an attack of Ménière's symptoms 3–6 weeks after she began to take it, and edema was often present as well. Pargyline has provided the best results to date; it has produced a moderately good antidepressant effect, only mild edema, and infrequent and mild attacks of Ménière's syndrome.

A second patient I treated also developed symptoms of tinnitus and vertigo, though no edema, while taking phenelzine, but these symptoms were relatively mild. I did not continue the phenelzine because the patient's psychiatric symptoms did not respond to it.

Appreciation of the possible relationship between symptoms of Ménière's disease and use of MAOIs may help to avoid unnecessary surgery. However, for patients who respond only to MAOIs, surgery may still be appropriate.

## REFERENCE

1. Laird LK, Lydiard RB: Imipramine-related tinnitus (letter). *J Clin Psychiatry* 1989; 50:146

JEFFREY A. MATTES, M.D.  
Princeton, N.J.

## Propranolol Withdrawal in Psychosis

SIR: We present the outcome of abrupt withdrawal from propranolol therapy in a woman with paranoid schizophrenia. The case illustrates the importance of tapering propranolol even when the dose is relatively low and the patient has no known hypertension or cardiac disease. The timing of our patient's reactions to the withdrawal supports some speculations about propranolol's therapeutic action in psychosis.

Ms. A, a 36-year-old white woman, had a history of chronic paranoid schizophrenia and migraine headaches. Following noncompliance with medical therapy, she developed an exacerbation of psychotic symptoms and required hospitalization. She was started on a regimen of 25 mg i.m. of fluphenazine decanoate every 2 weeks.

Within several days of beginning fluphenazine, Ms. A developed marked symptoms of akathisia. Propranolol was started and increased to 20 mg t.i.d. orally, which brought about resolution of her akathisia. At the same time, her psychotic perceptions continued a process of diminution that had begun before she started taking propranolol. At discharge she evidenced neither psychotic perceptions nor akathisia.

Ms. A remained clinically stable for the next 2½ months, until she abruptly stopped taking the propranolol. One week later, she experienced the onset of mounting anxiety and motor restlessness. A week after that, her auditory hallucinations recurred dramatically, and she was readmitted to the hospital. Within 6 days after the reinstitution of propranolol therapy, Ms. A's auditory hallucinations had disappeared, and her anxiety and motor restlessness had decreased markedly.

This patient's akathisia may have exacerbated her psychotic decompensation; however, this explanation fails to provide a complete explanation for the nature or time course of her symptoms. Ms. A's psychosis had begun responding to fluphenazine even before propranolol was first added to her medication regimen. Propranolol may have interacted with the fluphenazine to increase its therapeutic efficacy, by increasing either the serum level or the bioavailability of the fluphenazine. Unfortunately, Ms. A's serum fluphenazine levels were not measured.

Much has been written about the potential antipsychotic effects of propranolol (1), although typically these occur with doses about 10-fold greater than that taken by Ms. A. Propranolol has also been reported as a causative factor in the development of psychosis (2). Other reports have associated the abrupt withdrawal of propranolol with the development of severe mania or affective psychosis (3, 4). It may be that propranolol decreases psychosis in some patients while increasing it in others. Mechanisms involving multiple neurotransmitters, including  $\beta$ -adrenergic and/or noradrenergic receptors, may play a significant role in the acute symptoms of schizophrenia in patients such as Ms. A, as has been described in great detail by van Kammen and Gelernter (5).

## REFERENCES

1. Ananth J, Lin KM: Propranolol in psychiatry: therapeutic uses and side effects. *Neuropsychobiology* 1986; 15:20–27
2. Patterson JF: Propranolol-induced mania. *South Med J* 1984; 77:1603
3. Jouvent R, Baruch P, Simon P: Manic episode after propranolol withdrawal (letter). *Am J Psychiatry* 1986; 143:1633

4. McMahon T: Bipolar affective symptoms associated with use of captopril and abrupt withdrawal of pargyline and propranolol. *Am J Psychiatry* 1985; 142:759-760
5. van Kammen DP, Gelernter J: Biochemical instability in schizophrenia, I: the norepinephrine system, in *Psychopharmacology: The Third Generation of Progress*. Edited by Meltzer HY. New York, Raven Press, 1987

STEPHEN ROSENTHAL, M.D.  
Waltham, Mass.  
JAMES ELLISON, M.D.  
Cambridge, Mass.

### Schizotypal Personality and Brief Reactive Psychosis

SIR: A curious contradiction exists in the *DSM-III-R* section on brief reactive psychosis. Although schizotypal personality disorder is cited as making patients "particularly vulnerable" to brief reactive psychosis (p. 206), the definition of brief reactive psychosis specifically excludes patients with schizotypal personality disorder (p. 205). This contradiction may be a reflection of a deep historical division in how schizotypal personality has been conceptualized (1).

Current concepts of schizotypal personality are derived from descriptive clinical studies and genetic field studies. Clinical researchers have long described patients who seem to have quite mild forms of schizophrenia. These patients typically present with a combination of positive and negative symptoms that are of insufficient severity to warrant the diagnosis of schizophrenia. Outcome has been viewed as depending on environmental factors, and the risk of psychotic relapse under severe stress is acknowledged (2).

Geneticists have long searched for nonpsychotic individuals who are genetic variants of schizophrenic persons. The finding of the Danish Extended Family Study that nonpsychotic, so-called borderline schizophrenic individuals were clustered among the biological relatives of schizophrenic adoptees seemed to offer the wished-for link (3). This and subsequent genetic studies confirmed that social isolation, constricted affect, and other negative symptoms, rather than positive symptoms, were more specific to the affected biological relatives. Not surprisingly, a narrower definition of schizotypal personality disorder that deemphasizes positive symptoms has been favored by biogenetic researchers.

The *DSM-III* definition of schizotypal personality disorder was constructed from the diagnostic items used in the Danish Extended Family Study, a cross-validation with other studies, and a questionnaire to elicit the relevant clinical experiences of American psychiatrists. The result was a definition that includes both positive and negative symptoms. Subsequent clinical research has validated this broad definition (4).

The *DSM-III-R* definition of schizotypal personality disorder resembles the *DSM-III* definition. However, whereas *DSM-III* states that during periods of extreme stress patients with schizotypal personality disorder may develop transient psychotic symptoms, *DSM-III-R* qualifies this statement by saying that these psychotic symptoms "are usually insufficient in duration to warrant an additional diagnosis" (p. 341). Taken together with the exclusion clause in the definition of brief reactive psychosis, the diagnosis of schizotypal personality disorder in *DSM-III-R* becomes slightly narrower than the *DSM-III* version. Whether the current deemphasis of the potential for florid positive symptoms decreases or increases the clinical relevance of the schizotypal personality disorder construct is a question that awaits further research. In the meantime, patients with schizotypal personal-

ity disorder who become acutely psychotic under severe stress pose a diagnostic dilemma.

### REFERENCES

1. Kendler KS: Diagnostic approaches to schizotypal personality disorder: a historical perspective. *Schizophr Bull* 1985; 11:538-553
2. Meehl PE: Schizotaxia, schizotypy, schizophrenia. *Am Psychol* 1962; 17:827-838
3. Kety SS, Rosenthal D, Wender PH, et al: Mental illness in the biological and adoptive families of adopted individuals who have become schizophrenic: a preliminary report based on psychiatric interviews, in *Genetic Research in Psychiatry*. Edited by Fieve RR, Rosenthal D. Baltimore, Johns Hopkins University Press, 1975
4. Jacobsberg LB, Hymowitz P, Barasch A, et al: Symptoms of schizotypal personality disorder. *Am J Psychiatry* 1986; 143: 1222-1227

MARK OLFSON, M.D.  
New York, N.Y.

### Tarasoff and Threats of Patricide by a 9-Year-Old Boy

SIR: The *Tarasoff* ruling in 1976 has significantly influenced the practice of psychiatry (1). Interestingly, a search of the literature revealed no reports regarding the clinician's duty to protect when a child makes a specific homicidal threat. We present a case that illustrates the importance of the *Tarasoff* ruling as applied to latency-age children.

Adam, a 9-year-old third grader, was referred by his mother for an outpatient evaluation because of his recurrent threats to his father to blow his head off and to pour alcohol on his face and set him on fire. The mother had recently fled with the children from another state because of the father's chronic, severe physical abuse of her and the children. Adam had often been a witness to his father's violence and had watched him angrily place a pistol to his mother's head. On more than one occasion, he had physically attacked his father to try to defend his mother. Adam explained that he would have already shot his father, but "he blocked me from getting to the gun." Furthermore, he said that his father would be "gone forever" if he killed him. When the child voiced these threats, his mother subtly smiled.

After the first evaluation session, we learned that a warrant had been issued for the mother's arrest on kidnapping charges, and Adam and his two younger siblings were to be returned immediately to their father's custody. In following Appelbaum's three-step model for fulfilling the duty to protect (1), we 1) made a determination of dangerousness, 2) selected a course of action to protect the potential victim, and 3) implemented the plan. In this case, the seriousness of Adam's threats of patricide was evidenced by their explicit and persistent nature, the history of physical abuse of the child by the father, Adam's previous physical aggressiveness toward the intended victim, his repeated exposure to a model for violence (2), the availability of a gun (3), and the mother's covert encouragement (4) of the child's murderous threats toward his father. Our planned course of action was to notify the legal authorities and the father of these threats of patricide and the potential danger we felt they represented to the father if Adam were returned to his father's custody. We

implemented the first part of this plan by contacting the sheriff's office. They informed us that our alerting them to Adam's threats, in the context of their preliminary investigation, convinced them of the need to delay serving the warrant and returning Adam to his father until a further investigation of the alleged abuse by the father was possible. Thus, we were relieved of the immediate duty to warn the father.

The clinician must assess homicidal threats by a young child in the context of risk factors associated with violent childhood behavior and with attention to the child's developmental understanding of his actions and their consequences. This assessment may indicate the need to fulfill the duty to protect as outlined in the *Tarasoff* decision. Furthermore, the evaluation of dangerousness in a child, as demonstrated in this case, is pertinent to the developing subspecialty of forensic child psychiatry (5).

## REFERENCES

1. Appelbaum PS: *Tarasoff* and the clinician: problems in fulfilling the duty to protect. *Am J Psychiatry* 1985; 142:425-429
2. Lewis DO, Moy E, Jackson LD, et al: Biopsychosocial characteristics of children who later murder: a prospective study. *Am J Psychiatry* 1985; 142:1161-1167
3. Bender L: Aggression in children. *Res Publ Assoc Res Nerv Ment Dis* 1974; 52:201-208
4. Easson MB, Steinhilber RM: Murderous aggression by children and adolescents. *Arch Gen Psychiatry* 1961; 4:27-35
5. Benedek EP: Forensic child psychiatry: an emerging subspecialty. *Bull Am Acad Psychiatry Law* 1986; 14:295-300

WADE C. MYERS, M.D.  
ANTHONY CATERINE, M.D.  
Gainesville, Fla.

## Indiana Statute on the Duty to Protect

SIR: In their article "Statutory Approaches to Limiting Psychiatrists' Liability for Their Patients' Violent Acts," Paul S. Appelbaum, M.D., and associates (1) stated that the Indiana statute addressing the duty to protect does not require identifiable victims or an actual threat. They asserted that the statute is "disturbingly vague and likely to perpetuate confusion about when the duty to protect exists," since it requires action if the patient "evidences conduct or makes statements indicating an imminent danger that the patient will use physical violence or use other means to cause serious personal injury or death to others" (2).

Dr. Appelbaum and associates' conclusions arise from an incomplete reading of the statute, which states immediately before the provision just quoted that a duty exists when "the patient has communicated to the provider of mental health services an actual threat of physical violence or other means of harm against a reasonably identifiable victim or victims" (2). The language Dr. Appelbaum and his colleagues read as defining when a duty exists was introduced as an amendment by legislators who felt that mental health professionals had a duty to take action when the patient was acting in an obviously dangerous manner, even though no specific victim was identified. The term "imminent danger" indicates that a duty exists in those immediate situations which involve the observation, not the prediction, of dangerousness. This implies a distinction between situations involving the prediction of violence and those involving the observation of violence. The

difficulties in predicting violent behavior make it reasonable to place limits on the professional's liability. Such limits do not appear necessary when dealing with violent behavior that is observed. The Indiana statute attempts to address this distinction.

## REFERENCES

1. Appelbaum PS, Zonana H, Bonnie R, et al: Statutory approaches to limiting psychiatrists' liability for their patients' violent acts. *Am J Psychiatry* 1989; 146:821-828
2. Indiana Statutes Annotated Code, Section 34-4-12.4

MICHAEL J. MURPHY, PH.D.  
Terre Haute, Ind.

## Dr. Appelbaum and Associates Reply

SIR: The statute referred to by Dr. Murphy has two disjunctive clauses defining when a duty to protect potential victims arises. The first clause invokes the duty when "the patient has communicated to the provider of mental health services an actual threat of physical violence or other means of harm against a reasonably identifiable victim or victims." This clause is joined by an "or" to the second clause, which notes that the duty will arise when the patient "evidences conduct or makes statements indicating an imminent danger that the patient will use physical violence or use other means to cause serious personal injury or death to others."

Whatever the restrictive effect of the first clause, the benefits of limiting its requirements to actual threats and identifiable victims may be vitiated by the much broader language of the second clause. The latter leaves clinicians open to the allegation that, even in the absence of an overt threat, a patient's behavior or statements should have been recognized as indicating a danger sufficient to warrant preventive measures. Dr. Murphy's explanation of the intent of the provision, however accurate, stands in contrast to the indeterminate language of the statute, which does not require the observation of violent behavior or threatening statements on the part of the patient. Thus, pending judicial clarification of the statute, clinicians in Indiana remain uncertain about when the duty to protect arises. It is just such ambiguity that the majority of statutes limiting the duty to protect were designed to avoid.

PAUL S. APPELBAUM, M.D.  
Worcester, Mass.  
HOWARD ZONANA, M.D.  
New Haven, Conn.  
RICHARD BONNIE, J.D.  
Charlottesville, Va.  
LOREN ROTH, M.D., M.P.H.  
Pittsburgh, Pa.

## Long-Term Follow-Up of a Patient Who Received Electrical Stimulation for Chronic Vomiting

SIR: We report a 20-year follow-up of a case originally reported in 1970 by Galbraith et al. (1), who suggested that aversive conditioning by electrical stimulus was moderately effective in reducing chronic regurgitation in a mentally retarded boy. However, these authors concluded that symptom substitution occurred: the emetic behavior was replaced by



hyperactivity, masturbation, hair pulling, and self-injurious behavior.

In a comparison of behavior from September 1985 to March 1986, Svec (2) reported that this patient continued to display self-induced emesis predominantly in his residential setting. In his vocational setting, after October 1985, he did not display a single instance of regurgitation. A review of the medical, residential, and psychological files suggested that there had been no visible long-term side effects as a result of the use of electrical stimulation.

Most recently, in December 1988, this patient experienced his first complete month without emetic or regurgitative behavior in the residential setting. He continues to advance with respect to work, recreational, and leisure-time activities. His ratings on the Psychopathology Inventory for Mentally Retarded Adults, Ratings by Others Scale (3) suggest that there is now no psychopathology and no symptom substitution as originally reported by Galbraith et al.

From the evidence available it is not possible to make specific statements regarding the effectiveness of faradic stimulation in this case. A number of differing treatments, including extensive pharmacotherapy, and changing family status could have contributed to the improvement in this patient. The evidence does suggest that prolonged use of faradic stimulation has not resulted in negative side effects as previously thought. Future research will continue to monitor the progress of this patient, with particular emphasis on quality of life and psychiatric status.

#### REFERENCES

1. Galbraith DA, Byrick RJ, Rutledge JT: An aversive conditioning approach to the inhibition of chronic vomiting. *Can Psychiatr Assoc J* 1970; 15:311-313
2. Svec HJ: A study of self-injurious behavior of disabled clients within residential and vocational settings (doctoral dissertation). East Lansing, Michigan State University, 1988
3. Matson JL, Helsel WJ, Bellack AS, et al: Development of a rating scale to assess social skill deficits in mentally retarded adults. *Appl Res Ment Retard* 1983; 4:399-407

HENRY J. SVEC, PH.D.

F.J. BARRERA, PH.D.

Blenheim, Ont., Canada

HARVEY CLARIZIO, ED.D.

WALTER HAPKIEWICZ, PH.D.

CHRISTOPHER CLARK, PH.D.

LARRY MEHEADY, PH.D.

East Lansing, Mich.

#### Seasonal Birthrates and Schizophrenia

SIR: At least 31 studies have concluded that disproportionate numbers of schizophrenic individuals are born during the late winter and early spring months (January, February, and March). As documented by Boyd et al. (1), the excessive proportion of births during these months ranges from 6% to 35%.

We recently examined season of birth among psychiatric patients at the Durham Veterans Administration (VA) Medical Center. Computer-generated lists of all psychiatric patients admitted from Jan. 1, 1985, to Jan. 1, 1987, were sorted by admitting diagnosis and date of birth. After excluding all readmissions, we derived a group of 376 schizophrenic patients. In addition, we constructed two comparison groups. One consisted of all nonschizophrenic psychiatric

patients admitted during the same 2-year period; the second included all patients admitted to medical wards between Jan. 1, 1986, and Jan. 1, 1987. These comparison groups contained 867 and 2,529 individuals, respectively.

We found that 25.3% (N=95) of the schizophrenic patients were born during the period of late winter and early spring; 23.3% (N=202) and 24.8% (N=627), respectively, of the psychiatric and medical comparison patients were born in that period. Chi-square analyses showed no significant differences in late-winter/early-spring birthrates between the schizophrenic and the nonschizophrenic psychiatric patients ( $\chi^2=0.46$ ,  $df=1$ ,  $p=0.50$ ) or between the schizophrenic and the medical patients ( $\chi^2=0.02$ ,  $df=1$ ,  $p=0.89$ ).

We realize that there are several limitations to this exploratory study. First, the schizophrenic and comparison subjects were quite homogeneous, since they were all inpatients and veterans of the armed forces, and almost all were male. Second, our sample sizes were modest. Nevertheless, our results are of interest in light of reports that the late-winter/early-spring birth phenomenon is often less marked—indeed, is sometimes absent—for schizophrenic individuals born in Southern states and in nonurban environments (2). The authors of one report (3) speculated that neonatal exposure to viral agents—which occurs more frequently during the winter months, in crowded urban areas, and in the harsher weather of Northern states—may be one explanation for late-onset schizophrenia. While our study did not control for place of birth, the majority of patients at the Durham VA hospital are lifelong residents of rural or suburban North Carolina.

Thus, our study failed to demonstrate the late-winter/early-spring birth phenomenon in a predominantly Southern-born sample of schizophrenic patients. We hope that this report will prompt others to explore seasonal differences in birthrate between schizophrenic and nonschizophrenic individuals and the possible differences between schizophrenic individuals in Northern and Southern states. It is possible that certain etiologic factors in schizophrenia may correlate with climate, season, or geography.

#### REFERENCES

1. Boyd, JH, Pelter AE, Stewart W: Season of birth: schizophrenia and bipolar disorder. *Schizophr Bull* 1986; 12:173-186
2. Torrey EF, Torrey BB, Peterson MR: Seasonality of schizophrenic births in the United States. *Arch Gen Psychiatry* 1977; 34:1065-1070
3. Mednick SA, Machon RA, Huttunen MO, et al: Adult schizophrenia following prenatal exposure to an influenza epidemic. *Arch Gen Psychiatry* 1988; 45:189-192

PAMELA WOODARD, B.A.

MARC D. FELDMAN, M.D.

Durham, N.C.

#### Psychobiology and the Brain-Mind Relationship

SIR: The astonishing progress in psychobiology has led many to believe that once a neurobiological correlate of a psychological disorder is discovered, this correlate must also be the cause of the disorder.

But the discovery that a chemical and/or electrophysiological abnormality is frequently or even regularly found in conjunction with a given psychological disorder proves only that

the pathological brain process accompanies the psychic disorder more or less regularly. It does not prove any causal relationship—only a highly significant statistical one.

The substantive nature of the relation itself remains fundamentally obscure as long as the brain-mind interaction is not understood (1, 2). We do not know just how a causal relation between the two might operate. We merely postulate that it must exist.

The concept of psychosomatic disease implies a causal nexus in the mind-brain direction: a psychological process influences a somatic target through its correlated brain process, which itself would have to be called psychosomatic. How? We don't know. But if causality across the brain-mind gap exists, it seems to work in both directions.

An argument for the predominant causal role of brain physiopathology in psychological disorders is that because a drug is effective in ameliorating such a disorder (obsessive-compulsive disorder, for example) and because it alters brain physiology, the older psychogenic theories are suspect, if not irrelevant. But this is jumping to a conclusion, for there is an alternative. It may be wrong to think in terms of two qualitatively different, separate, yet somehow interacting processes, one organic, the other mental. Instead, we may be dealing with a single two-sided process whose internal dynamics remain unknown. From the point of view of structural logic (3, 4), there is a fundamental difference between the two views. If the brain disorder were but a component part of one pathological process, attacking it by means of a drug would be attacking the whole and therewith also the other (psychological) part, and vice versa: if a neurosis were ameliorated by psychotherapy, this would have to alter the brain physiopathology.

Neither therapeutic approach would permit an inference about the original cause of the psychophysiopathology. If a patient develops a skin rash because he is allergic to an indispensable medication, and the rash is treated topically, the success of the dermatological treatment does not prove that the cause of the rash was located in the skin. By the same token, the success of a drug treatment of a neurosis does not of itself imply that the cause of the disorder was physiological.

In any case, either hypothesis remains intrinsically empty as long as we have no concrete idea of the nature of either the interaction of two totally heterogeneous processes or of the internal dynamics of the hypothesized whole process.

#### REFERENCES

1. Levy E: Some thoughts on the mind-body problem. *Perspect Biol Med* 1980; 513-525
2. Levy E: A note on the mind-brain problem. *Gestalt Theory* 1988; 10:129-133
3. Wertheimer M: *Productive Thinking*. New York, Harper & Brothers, 1959
4. Levy E: A problem in thinking. *Psychol Rep* 1981; 49:219-236

ERWIN LEVY, MD.  
New York, N.Y.

#### Importance of Consultation-Liaison Psychiatry

SIR: The article by Cheryl F. McCartney, M.D., and associates (1) about the effectiveness of liaison in an oncology program is a welcome addition to the literature. At a time when the importance of liaison has been questioned, the article provides information to help the field of consultation-

liaison psychiatry sort out the facts from the rhetoric. The conclusions of the article confirm our own earlier research on two general medical units (2, 3), and together the three articles make a persuasive statement. They show that a liaison component designed to help nonpsychiatric staff members identify and refer patients with psychiatric disorders can effectively reach and treat a segment of the medical inpatient population who have concurrent psychiatric disorders and who would otherwise be denied the services they require.

The articles also suggest that exposure to the psychiatric disorders often seen on a consultation-liaison service, such as various forms of delirium, conversion reactions, adjustment disorders, and psychosomatic illnesses, is dramatically increased with the liaison program. Experience with these kinds of patients and syndromes is essential if we are to meet our educational objectives for psychiatry residents and Fellows in consultation-liaison psychiatry.

It is likely that a large portion of the resistance of nonpsychiatric physicians to identifying and referring medical patients with concurrent psychiatric symptoms is inherent in general hospital practice, and the assistance of a psychiatric liaison will be necessary to effectively reach this population. In the long run, a psychiatric liaison component on a consultation-liaison service helps the nonpsychiatric physician achieve the objective of providing excellent comprehensive clinical care, an ideal common to all physicians. Further work is needed to help define the different functions of liaison and to specify the techniques needed to achieve defined goals in different inpatient settings. The work of Dr. McCartney and colleagues is a valuable contribution in this direction.

#### REFERENCES

1. McCartney CF, Cahill P, Larson D, et al: Effect of a psychiatric liaison program on consultation rates and on detection of minor psychiatric disorders in cancer patients. *Am J Psychiatry* 1989; 146:898-901.
2. Torem M, Saravay SM, Steinberg H: Psychiatric liaison: benefits of an "active" approach. *Psychosomatics* 1979; 20:598-611
3. Steinberg H, Torem M, Saravay SM: An analysis of physician resistance to psychiatric consultations. *Arch Gen Psychiatry* 1980; 37:1007-1012

STEPHEN M. SARAVAY, M.D.  
HERBERT STEINBERG, M.D.  
New Hyde Park, N.Y.  
MOSHE TOREM, M.D.  
Akron, Ohio

#### Multiple Personality Disorder: The New "Royal Road"?

SIR: After treating a considerable number of patients who have multiple personality disorder, I am still struck by the play-acting quality of many of these patients. It's as if the whole presentation is a monumental "put-on." When, with an adult patient, you are sitting on the floor playing blocks with a "child," or with a male patient, you are discussing mother-daughter issues with his "twin sister" who occupies the same body, the experience requires a flexibility that is tantamount to suspending formal logic concerning the constancy of the patient's sex and age. Moreover, when you consult with colleagues or admit the patient to an inpatient setting, a debate about the validity of multiple personality disorder is inevitably engendered. Schizophrenia and bipo-

lar disorder are not argued about, but multiple personality disorder is. Alternative diagnoses are presented, which invariably include borderline personality disorder with histrionic or antisocial features and, often, factitious disorder or malingering.

What is so provocative about the symptoms of multiple personality disorder that so many practitioners find it "unbelievable"? I suggest it is nothing more complicated than their unfamiliarity with dissociative defenses, coupled with an atavistic fear of being in a situation where there is no guarantee that the person you are sitting with will not change in front of your eyes into someone else, possibly a dangerous person with whom you have no secure therapeutic alliance. This is not the realm of countertransference. This is the disorientation of not knowing from moment to moment with whom you are talking. Very disconcerting.

Patients with multiple personality disorder "live" the past and "are" their identifications. Being witness to these phenomena is rather engaging—maybe too much so for therapists who are more comfortable with hearing about these matters than with being there for the action. And then there is the matter of amnesia, an excellent defense against overwhelming trauma and a sequela of the switching process itself. Yet this, too, is challenged as being secondary gain or a manipulation by the patient to disavow responsibility for his or her difficulties. What a Calvinistic yardstick by which to judge the worthiness for treatment of a victim of extreme childhood abuse!

However, my purpose here is not to prove the validity of multiple personality disorder, but, rather, to invite more scientific inquiry into the realm of dissociation by "non-believers." Multiple personality disorder phenomena are presented vividly and overtly and thus make possible the firsthand examination of psychic functions, with less need to speculate on processes that are covert and disguised. You can *see* the identifications; you can *hear* the traumatic scenarios.

My hope is that research on multiple personality disorder can be viewed by more of our psychiatric colleagues not as esoteric or second-class or "flaky" but, rather, as first-class, mainstream, and possibly even the new "royal road" to the conscious/unconscious.

Jump aboard. Read the new books on multiple personality disorder (1–3). Go to a conference on the subject. The more serious thinkers there are in this realm of trauma psychology, the more rapid the advances will be—not just for patients with multiple personality disorder but for all our patients who have had a rough go of it.

#### REFERENCES

1. Putnam FW: *Diagnosis and Treatment of Multiple Personality Disorder*. New York, Guilford Press, 1989
2. Braun BG (ed): *Treatment of Multiple Personality Disorder*. Washington, DC, American Psychiatric Press, 1986
3. Kluft RP (ed): *Childhood Antecedents of Multiple Personality*. Washington, DC, American Psychiatric Press, 1985

NEAL A. KLINE, M.D.  
*La Jolla, Calif.*

#### Photophobia in Other Disorders as Well as Depression

SIR: Recent letters to the Editor (1, 2) have examined the behavior of depressed patients who exhibit light avoidance when their mood is low. Gerbaldo (1) suggested that photo-

phobic behavior might have an effect on photosensitive neuroendocrine processes, and Signer and Lapierre (2) proposed ingeniously that dysfunction of the autonomic innervations of the papillary sphincter and ciliary muscle may cause the behavior. Photophobic behavior manifested by the wearing of tinted eye glasses by patients presenting to general medical hospital clinics has often been noted by physicians in the United Kingdom and has been taken as an indication of psychopathology (3). It was recently shown that general medical patients without ocular pathology who choose to wear tinted glasses score more highly than control subjects matched for age, sex, and diagnosis on indexes of pathological personality measured by self-report inventory (4). None of these patients had primary psychiatric diagnoses, and although depressive symptoms were repeatedly elicited, their photophobia was associated with more widespread personality disturbance.

I wonder whether this is a peculiarly English observation or whether it applies across the Atlantic.

#### REFERENCES

1. Gerbaldo H: Depression and photophobic behavior (letter). *Am J Psychiatry* 1988; 145:1479–1480
2. Signer SF, Lapierre YD: Photophobia and depression (letter). *Am J Psychiatry* 1989; 146:1355–1356
3. Trevor-Roper PD, Curran PV: *The Eye and Its Disorders*, 2nd ed. Oxford, England, Blackwell, 1984
4. Howard RJ, Valori RM: Hospital patients who wear tinted spectacles—physical sign of psychoneurosis: a controlled study. *J R Soc Med* 1989; 82:606–608

DR. ROBERT HOWARD  
*London, England*

#### Role of Psychotherapy in Bipolar Disorder

SIR: In a Special Article, "Alternatives to Lithium for Preventive Treatment of Bipolar Disorder" (1), Robert F. Prien, Ph.D., and Alan J. Gelenberg, M.D., made reference to psychotherapy briefly, stating that such intervention may bring about "improved compliance in taking medication and better recognition of early signs of an emerging episode" (p. 845). While the authors' focus was on the pharmacological treatment of the condition, nothing whatever was said of the efficacy of combining drugs with psychotherapy whenever possible to promote dynamic understanding of intrapsychic conflict and thereby prevent acute recurrences. Nor was there any acknowledgment of the contributions of Ostow, Wolpert, Pao, and others who have taken this approach and accumulated considerable experience in the long-term psychoanalytic therapy of affective disorders.

On the basis of an extensive survey, Coryell et al. (2) noted a familial relationship between high achievement and bipolar illness before concluding that "the nature and reasons for this association remain fertile questions for future research" (p. 987). Overlooked completely was the pioneering work of Mabel Blake Cohen and her group at Chestnut Lodge (3), who found, after closely observing the families of manic-depressive patients, that these individuals had been designated, generally by their mothers, "as the chief carrier of the burden of winning prestige for the family" and were, therefore, often exceedingly ambitious.

Has the biological model become so predominant in the field of psychiatry today that we can afford to ignore the

clinical data, gathered painstakingly over the years by paying close attention to the vicissitudes of early development and the role of unconscious processes in the evolution of severe psychopathology?

## REFERENCES

1. Prien RF, Gelenberg AJ: Alternatives to lithium for preventive treatment of bipolar disorder. *Am J Psychiatry* 1989; 146:840-848
2. Coryell W, Endicott J, Keller M, et al: Bipolar affective disorder and high achievement: a familial association. *Am J Psychiatry* 1989; 146:983-988
3. Cohen MB, Baker G, Cohen RA, et al: An intensive study of twelve cases of manic-depressive psychosis. *Psychiatry* 1954; 17:103-137

JAMES W. HAMILTON, M.D.  
Santa Fe, N. Mex.

### P.T. Barnum and the Borderline Personality Disorder Muddle

SIR: Frederick T. Melges, M.D., and Marvin S. Swartz, M.D. (1) provided an interesting thesis concerning issues of regulation of interpersonal distance in patients with borderline personality disorder. By formulating the problem in an interpersonal sphere, they created an organized way of looking at the seeming instability of such individuals. The clinical applications of such a reformulation are readily apparent, as the "stable instability" can be explained to both patient and significant others and be addressed directly.

A significant issue is raised, however, by the approach of attaching (pun intended) the concept of oscillation and the cybernetic model to borderline personality disorder specifically. What Drs. Melges and Swartz described is a dimension of interpersonal behavior that underlies all human interpersonal behavior and that has been well documented in the empirical psychological literature. Benjamin (2) has contributed substantially both to empirical and methodological advances in the area of measurement of interpersonal distance and to the issue of oscillations in attachment (3).

However, the most unfortunate effect of presenting the model of Dr. Melges and Dr. Swartz as representative of, or differentially applicable to, borderline personality disorder is the "Barnum effect" described by Meehl (4). Meehl suggested this term to denote the stating "of trivial things that are true of practically all psychiatric patients, or sometimes of practically all human beings" (pp. 236-237)—a good way to enhance one's credibility with the population at large. I would argue, however, that Drs. Melges and Swartz have said something important, not trivial, which is applicable to human beings but not differentially applicable to the nosological entity called borderline personality disorder.

It is important, therefore, also to note that ascribing to an individual characteristics which have a high base rate in the population (i.e., in psychiatric patients) will have dire consequences when used as diagnostic criteria, by actually decreasing the reliability of the diagnosis. Dr. Melges and Dr. Swartz did not take a stand with respect to "other models or levels of explanation" than their own thesis of problematic

"distance regulation." Thus, we now have another "ad hoc" and "plausible sounding" explanation (4, pp. 261-262) for a disorder well-known to be lacking even quasi-definitive criteria and for which ad hoc explanations abound. At present, in the study of borderline personality disorder, we have oscillations between the age-old problems of Procrustes (5) and the unicorn (6). As with Procrustes, the data are forever being altered to fit the theory; as with the unicorn, the theories are forever being transformed to fit the available data. The borderline muddle will not be clarified without cognizance of such philosophical issues.

## REFERENCES

1. Melges FT, Swartz MS: Oscillations of attachment in borderline personality disorder. *Am J Psychiatry* 1989; 146:1115-1120
2. Benjamin LS: Structural analysis of social behavior. *Psychol Rev* 1974; 81:392-425
3. Benjamin LS: Structural analysis of differentiation failure. *Psychiatry* 1979; 42:1-23
4. Meehl PE: Why I do not attend case conferences, in *Psychodiagnosis: Selected Papers*. New York, WW Norton, 1973
5. Nunnally JC: *Psychometric Theory*, 2nd ed. New York, McGraw-Hill, 1978
6. Cole LC: Biological clock in the unicorn. *Science* 1957; 125:874-876

VICTOR S. ALPHER, PH.D.  
Houston, Tex.

### Dr. Swartz Replies

SIR: In the literature on interpersonal behavior, Dr. Alpher directs the reader to Dr. Benjamin's work, which I also recommend for its empirical strength.

To meet Dr. Alpher's standard of formulations "differentially applicable to . . . borderline personality disorder," we must assume, without empirical support, that a mutually exclusive categorical nosology for personality disorders is correct and that clinical formulations must adhere to such a categorical nosology. Our paper did not assume that a categorical nosology is correct, and nosologic disputes about personality disorders were beyond the scope of the paper.

Dr. Melges and I did discuss clinical formulations that are potentially useful with patients who have diagnoses of borderline personality disorder. These formulations are not diagnostic criteria. If our remarks, as Dr. Alpher suggests, "will have dire consequences when used as diagnostic criteria," it will be the result of a misinterpretation of the paper. His reference to the "Barnum effect" conjures up a disdainful image of the clinician as huckster. The "borderline personality disorder muddle" is no more the fault of clinicians than of empiricists; it is the state of our shared scientific domain. Its resolution will come from an iterative exchange between clinical theory and empirical investigation, which *will*, I hope, heed Dr. Alpher's cautions about Procrustes and the unicorn.

MARVIN S. SWARTZ, M.D.  
Durham, N.C.

*Reprints of letters to the Editor are not available.*



### Position Statement Opposing Mandatory Name Reporting of HIV-Seropositive Individuals

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*This statement was proposed by the Commission on AIDS.<sup>1</sup> It was approved by the Board of Trustees in September 1989 and the Assembly of District Branches in November 1989.*

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APA opposes laws or regulations requiring the names of HIV-seropositive individuals to be reported to public health officials. Although permissive reporting policies, designed to protect third parties, are warranted under some circumstances, *mandatory name-*

*reporting* requirements would breach patient confidentiality without achieving any significant practical benefit to the public health. Mandatory reporting does not assure successful implementation of contact-tracing programs because the tracing of contacts ultimately depends on the voluntary cooperation of infected individuals. Moreover, current data indicate that if name reporting of HIV-seropositive individuals were legally required, many people would be discouraged from seeking HIV testing and would not have the benefit of early access to counseling and treatment.

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<sup>1</sup>The Commission on AIDS includes Stuart E. Nichols, M.D. (chairperson), Richard Lonsdorf, M.D., James Krajewski, M.D., Francisco Fernandez, M.D., Robert Kertzner, M.D., Jeffrey Akman, M.D., Alexandra Beckett, M.D., Joyce Johnson, D.O., Janice Hutchinson, M.D., Eric Kaplan, M.D., David Rosmarin, M.D. (liaison from the American Academy of Psychiatry and the Law), Douglas Sargent, M.D. (Board liaison), Peter Sack, M.D. (Assembly liaison), Richard Bridburg, M.D. (Assembly liaison), Ruth Herman, M.D. (APA/Burroughs Wellcome Fellow), and Eric Bing, M.D. (APA/NIMH Fellow).

## Guidelines Regarding Possible Conflict Between Psychiatrists' Religious Commitments and Psychiatric Practice

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*The guidelines were prepared by the Committee on Religion and Psychiatry.<sup>1</sup> They were approved by the Assembly in November 1989 and by the Board of Trustees in December 1989.*

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- I. Psychiatrists should maintain respect for their patients' beliefs.
  - A. It is useful for clinicians to obtain information on the religious or ideologic orientation and beliefs of their patients so that they may properly attend to them in the course of treatment.
  - B. If an unexpected conflict arises in relation to such beliefs, it should be handled with a concern for the patient's vulnerability to the attitudes of the psychiatrist. Empathy for the patient's sensibilities and particular beliefs is essential.
  - C. Interpretations that concern a patient's beliefs should be made in a context of empathic respect for their value and meaning to the patient.
- II. Psychiatrists should not impose their own religious, antireligious, or ideologic systems of beliefs on their patients, nor should they substitute such beliefs or ritual for accepted diagnostic concepts or therapeutic practice.
  - A. No practitioner should force a specific religious, antireligious, or ideologic agenda on a patient or work to see that the patient adopts such an agenda.
  - B. Religious concepts or ritual should not be offered as a substitute for accepted diagnostic concepts or therapeutic practice.

### APPENDIX 1. Background and Examples

In processing the issues involved, the APA Committee on Religion and Psychiatry concluded that some version of these difficulties is potentially present, at least subtly, in any psychiatrist's practice. The committee concurred that many psychiatrists take these issues and

their solutions to be self-evident and easily subsumed under existing ethical formulations.

Many other practitioners, however, were of the opinion that this category of antitherapeutic ethical violation occurs frequently enough and with sufficiently important negative consequences to the individual patient and to the psychiatric profession to merit a specification of ethical guidelines.

The following brief examples illustrate the kinds of problems that may arise when strong beliefs are interjected into a clinical practice. These examples are among those which were addressed to the committee.

1. A psychiatrist began treating a homosexual man for depression. The initial focus of treatment was on the patient's depression, as the patient did not seek treatment for his sexual orientation. After the depression lifted, the issue of homosexuality became more prominent in the therapy. Only after considerable therapeutic investment on the patient's part did the therapist indicate that he regarded the patient's sexual orientation to be sinful.

2. A devoutly religious psychiatrist pressed a severely depressed nonreligious patient to engage with her in prayer at the time of an initial therapeutic encounter. The patient had not anticipated a religious component to the therapy and was not accustomed to religious practice. She was quite troubled to find herself drawn into it, and her symptoms were aggravated.

3. A group of radical socialist psychiatrists conducted a medical clinic dedicated to implementing their ideologic system. They explained to a series of troubled patients that the source of their symptoms lay primarily in their political plight and pressed them into participating in a political campaign without informed consideration of alternative therapy.

4. A psychiatrist provided interpretations to a devoutly religious man. In doing this, however, she denigrated his long-standing religious commitments as foolishly neurotic. Because of the intensity of the therapeutic relationship, the interpretations caused great distress and appeared related to a subsequent suicide attempt.

---

<sup>1</sup>The members of the Committee on Religion and Psychiatry are Marc Galanter, M.D. (chairperson), Herzl Robert Spiro, M.D. (vice-chairperson), Paul Cecil Mohl, M.D., Paula C. Dobbs-Wiggins, M.D., George Tryon Harding, Jr., M.D. (consultant), Ruth Tiffany Barnhouse, M.D. (corresponding member), Richard J. Thurrell, M.D. (Assembly liaison), and Charles Van Tuyl (APA/Burroughs Wellcome Fellow).



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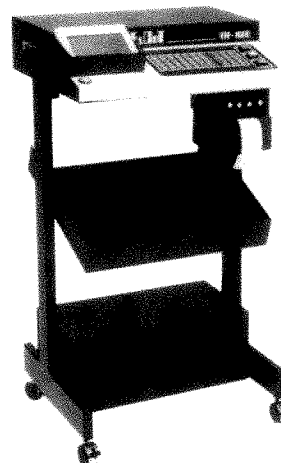
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*(Continued from page A26)*

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June 27–30, 1st International Congress on Behavioral Medicine, Uppsala. Contact Ulla Wallin, Department of Clinical Psychology, University of Uppsala, P.O. Box 1225, S-751 42, Uppsala, Sweden.

June 27–July 1, annual meeting, Association of Professional Sleep Societies, Minneapolis. Contact Lori J. Lingl, Meeting Coordinator, 604 Second Street, SW, Rochester, MN 55902; 507-287-6006.

## JULY

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July 2–7, 6th Prague International Conference on Psychological Development and Personality Formative Processes, Prague. Contact The 6th Prague International Conference, Institute of Psychology, Husova 4, 110 00 Prague 1, Czechoslovakia.

July 4–8, 2nd International Conference on The Future of Adult Life, Leeuwenhorst Congress Centre, The Netherlands. Contact Mike Featherstone, Centre for the Study of Adult Life, Department of Administrative and Social Studies, Teesside Polytechnic, Middlesbrough, Cleveland TS1 3BA, United Kingdom; (0642) 218121, ext. 4313.

July 5–7, 1st International Conference on Psychology and Performing Arts, London. Contact Dr. Glenn Wilson, Institute of Psychiatry, London SE5 8AF, United Kingdom; (01) 703-5411, ext. 3254.

July 16–20, 10th International Congress, International Association for Cross-Cultural Psychology, Nara, Japan. Contact Saburo Iwawaki, Graduate School of Education, Hyogo Kyoiku Diagaku, Yashirocho Katogun Hyogo, 673 Japan.

July 16–20, 12th International Congress of Child Psychiatry, International Association for Child and Adolescent Psychiatry and Allied Professions, Kyoto, Japan. Contact Professor Kosuke Yamazaki, c/o Dr. Reimer Jensen, Borups, alle 179, 2400 Copenhagen NV, Denmark.

July 18–22, annual meeting, National Alliance for the Mentally Ill, Chicago. Contact Laurie M. Flynn, 2101 Wilson Boulevard, Suite 302, Arlington, VA 22201; 703-524-9094.

July 19–22, annual meeting, Autism Society of America, Seattle. Contact Thomas Nerney, 1234 Massachusetts Avenue, NW, Suite C1017, Washington, DC 20005; 202-783-0125.

July 23–27, annual meeting, International Transactional Analysis Association, Brussels. Contact Susan Sevilla, 1772 Vallejo Street, San Francisco, CA 94123; 415-885-5992.

July 24–28, 24th CIOMS Conference on "Genetics, Ethics and Human Values: Humane Genome, Mapping, Screening & Treatment," Tokyo. Contact Multinational Meetings Information Services, P.O. Box 5090, NL-1007 AB Amsterdam, The Netherlands; 3120/684451.

July 31–August 5, 2nd Congress on Human Rights, Medicine and Law, Bophuthatswana. Contact International Centre of Medicine & Law, University of Bophuthatswana, P.O. Box 4182, Bophuthatswana, Southern Africa; 27 (0) 140 842470-1.

## AUGUST

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August 11–15, annual meeting, American Sociological Association, Washington, D.C. Contact William V. D'Antonio, 1722 N Street, NW, Washington, DC 20036; 202-833-3410.

August 18–24, 5th European Congress of Hypnosis in Psychotherapy and Psychosomatic Medicine, Konstanz. Contact Walter Bongartz, University of Konstanz, 750 Konstanz, Federal Republic of Germany.

August 20–23, 9th International Congress, Medical Informatics Europe 90, "Health Added Value," Glasgow. Contact Dr. J. Bryden, Consultant in Health Information, Greater Glasgow Health Board, Department of Public Health Medicine, McLeod Street, Glasgow G4 0RA, Scotland; 041 553 1833, ext. 222.

August 20–24, 21st Congress, International Society of Psychoneuroendocrinology, Buffalo. Contact Uriel Halbreich, M.D., Department of Psychiatry, State University of New York at Buffalo, 462 Grider Street (K-Annex), Buffalo, NY 14215; 716-898-5088.

August 23–26, World Psychiatric Association Regional Symposium—"Etiology of Mental Disorder," organized by the Department of Psychiatry, University of Oslo. Contact Prof. Einar Kringle, WPA Regional Symposium Programme Committee, Department of Psychiatry, University of Oslo, P.O. Box 85, Vinderen, N-0319 Oslo 3, Norway; 47 2 146590.

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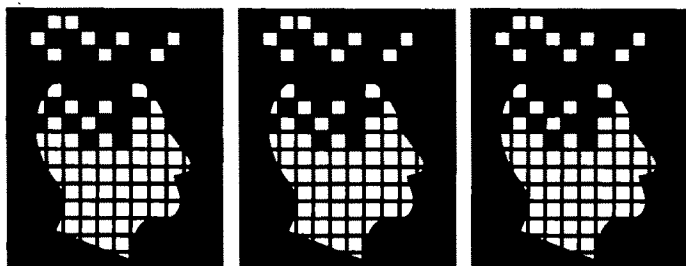
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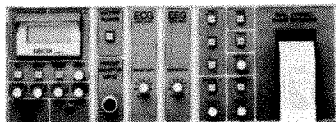
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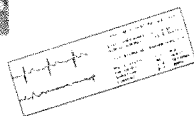
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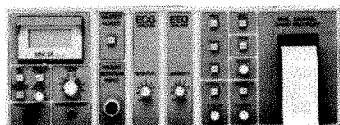
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These are usually overview articles that bring together important information on a topic of general interest to psychiatry. Authors who have ideas for such articles are advised to check with the Editorial Office to ensure that a similar work has not already been submitted. Special Articles may not exceed 7,500 words (no more than 25 double-spaced pages—including an abstract of no more than 100 words, tables, and figures) and may not include more than 100 references.

### Regular Articles

Regular Articles are original communications of scientific excellence in psychiatric medicine and advances in clinical research. Regular Articles contain no more than 3,800 words, including an abstract of no more than 100 words, references, tables, and figures. A table or figure that fills one-half of a vertical manuscript page equals 100 words of text; one that fills one-half of a horizontal page equals 150 words. Articles that exceed 3,800 words will be returned unreviewed to the authors.

### Clinical and Research Reports

Clinical and Research Reports may contain no more than one table and a maximum of 10 references; figures may not be used. Papers may contain a **maximum** of 1,300 words, including an abstract of no more than 40 words, references, and an optional table (estimate 15 words per reference, 100 words for a double-spaced table that fills one-half of a vertical page, and 150 words for a double-spaced table that fills one-half of a horizontal page). These articles present 1) new research findings, 2) data from pilot studies, 3) worthwhile

replication studies, and 4) clinical studies involving a number of patients. Essays, program descriptions, literature reviews, and single case reports do not meet the criteria for this section. Submissions that exceed 1,300 words or contain figures will be returned to the author.

### Other Sections

**Letters to the Editor.** Brief letters (maximum of 500 words and 5 references; no tables or figures) will be considered if they include the notation "for publication." Letters critical of an article published in the *Journal* will automatically be sent to the authors for reply. Because of space limitations not all letters can be printed. The *Journal* will notify authors about the disposition of their letters but does not return those that are not published. A letter must be signed by all of its authors. All letters will be edited; edited letters will not be sent to authors for approval. Letters must be typed **double-spaced** throughout on 8½×11 inch paper; three copies are required. Letters that do not meet these specifications will be returned for revision. Reprints are not available. **Single case reports except for detailed longitudinal studies should be submitted as Letters to the Editor.** Case reports submitted as Letters to the Editor will be peer reviewed.

**Book Forum.** Books for review may be sent to the Book Forum Editor, Nancy C. Andreasen, M.D., Ph.D., University of Iowa College of Medicine, 500 Newton Rd., Iowa City, IA 52242. Book reviews are usually solicited by the Book Forum Editor. Authors interested in reviewing a particular book should communicate directly with Dr. Andreasen. Reprints of reviews are not available.

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All parts of the manuscript, including case reports, quotations, references, and tables, must be **double-spaced** throughout. Manuscripts must be typed in upper- and lowercase on one side only of 8½×11 inch **nonerasable** bond paper. All four margins must be 1½ inches. The manuscript should be arranged in the following order, with each item beginning a new page: 1) title page, 2) abstract, 3) text, 4) references, and 5) tables and/or figures. All pages must be numbered.

## STYLE SPECIFICATIONS

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**Title.** The title should be informative and as brief as possible. Two-part titles should be avoided.

**By-line.** Authors listed in the by-line should be limited to principal researchers and/or writers; collaborators may be acknowledged in a footnote. Authors' first names are preferred to initials. Degrees should be included after each author's name.

**Previous presentation.** If the paper has been presented at a meeting, please give the name of the meeting, the place, and the date.

**Location of work and address for reprints.** Provide the department, institution, city, and state where the work was done. Include a full address for the author who is to receive reprint requests.

**Acknowledgments.** Grant support should be acknowledged in a separate paragraph and should include the full



name of the granting agency and grant number. The *Journal* does not allow acknowledgment of persons involved with the preparation or typing of manuscripts. Acknowledgment of individuals involved with the scientific content of the work should not exceed four typed lines. Drug company support of any kind must be acknowledged.

### Abstract

The abstract is a single paragraph no longer than 100 words for Special Articles and Regular Articles and no longer than 40 words for Clinical and Research Reports.

### Text

Authors should use the active voice and first person; headings and subheadings should be inserted at reasonable intervals. Footnotes to text may not be used, and summaries are usually unnecessary.

**Research design and statistics.** The following information regarding research design should be included: 1) a clearly stated hypothesis, 2) the names of the statistical tests used, 3) whether tests were one- or two-tailed, and 4) what test was used for each set of data. Reporting of standard deviations, rather than standard errors of the mean, is required. Statistical tests that are not well known should be referenced. All significant and important nonsignificant results must include the test value, degree(s) of freedom, and probability. For example, "The analysis of variance indicated that those who abstained from coffee had significantly higher course grades than those who did not abstain ( $F=4.32$ ,  $df=3$ ,  $17$ ,  $p<0.05$ ).\" Reviewers will evaluate the appropriateness of the analyses.

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2. Kaplan HI, Sadock BJ (eds): *Comprehensive Textbook of Psychiatry*, 4th ed, vol 2. Baltimore, Williams & Wilkins, 1985
3. Fyer AJ, Manuzza S, Endicott J: Differential diagnosis and assessments of anxiety: recent developments, in *Psychopharmacology: The Third Generation of Progress*. Edited by Meltzer HY. New York, Raven Press, 1987

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Tables should be double-spaced, no wider than 120 type-writer characters, including spaces, and no longer than 70 lines. Values expressed in the same unit of measurement should read down, not across; when percentages are given, the appropriate numbers must also be given.

#### Figures

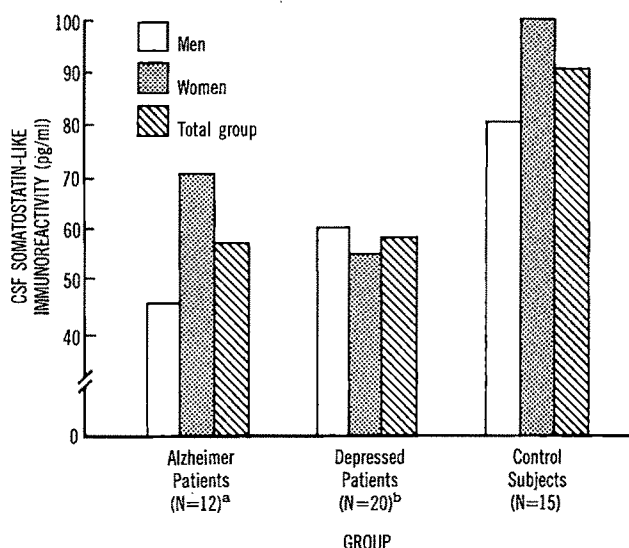
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**Format.** Figures are visual expressions of data trends or relationships. Figures that represent numerical data which could be expressed more succinctly or clearly in tabular form should be converted to tables. Line graphs should show change in continuous variables; comparisons of like values in different groups should be presented as bar graphs. Graphs containing stacked bars are unacceptable; the different segments of each bar should be presented side by side.

**Lettering.** Figure type should be sans serif and should be 7 points or larger after the figure is reduced; most figures taking up the width of a vertical manuscript page are reduced to a width of 19.5 picas (3¼ inches), and those requiring a horizontal manuscript page are usually reduced to 40.5 picas (6¼ inches). When space on the horizontal axis is insuffi-

**FIGURE 1. Mean CSF Somatostatin Levels of Patients With Alzheimer's Disease, Older Depressed Patients, and Age-Matched Control Subjects**



<sup>a</sup>Significant difference between men and women ( $t=1.81$ ,  $df=10$ ,  $p<0.05$ ) and between the total Alzheimer's disease group and the total control group ( $t=2.49$ ,  $df=25$ ,  $p<0.01$ ).

<sup>b</sup>Significant difference between the total depressed group and the total control group ( $t=2.75$ ,  $df=33$ ,  $p<0.005$ ).

cient, headings may be placed diagonally on the axis. Main headings should consist of upper-case letters only, subheadings of upper- and lower-case, and other type (e.g., keys, flow chart segments) of lower-case with only an initial upper-case letter. All parenthetical material should be lower-case. Do not use idiosyncratic abbreviations.

**Other.** The following are additional specific requirements. Please refer to the example given above.

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2. The heading for the vertical axis of a graph should run vertically along the axis, not horizontally at the top or bottom. Headings for the horizontal axis should appear below that axis, not at the top of the graph.

3. Error bars should not be used.

4. Do not extend the vertical or horizontal axis of a graph beyond the point needed for the data shown.

5. The vertical axis should generally begin at zero; to save space, a double slash may take the place of an unused portion of the vertical axis.

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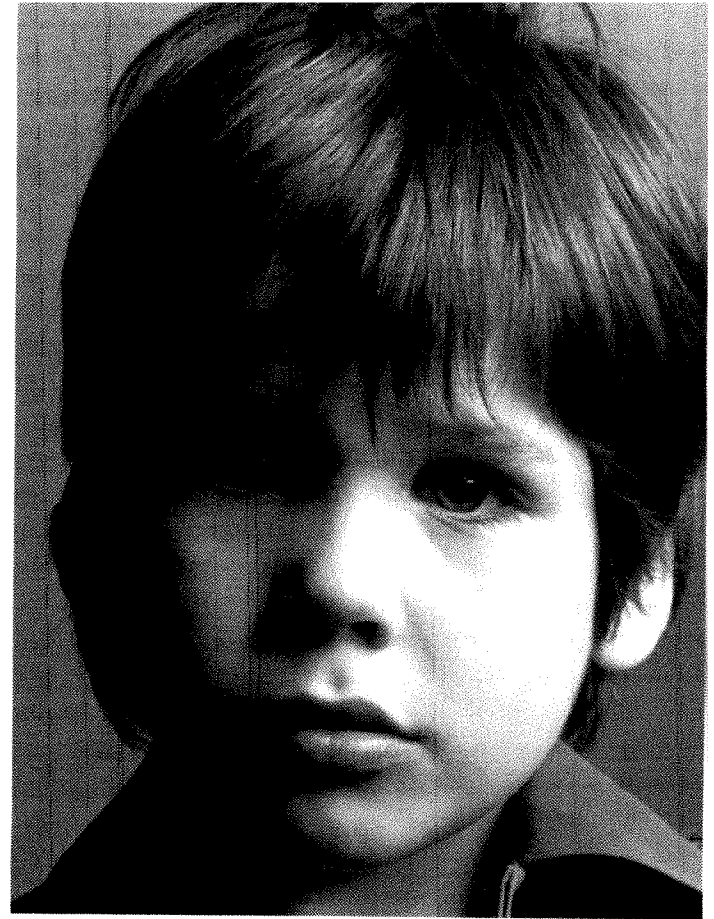
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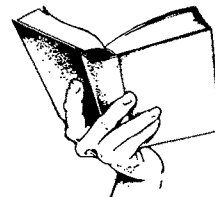
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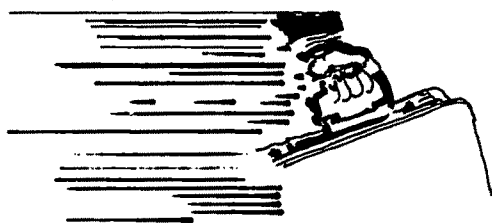
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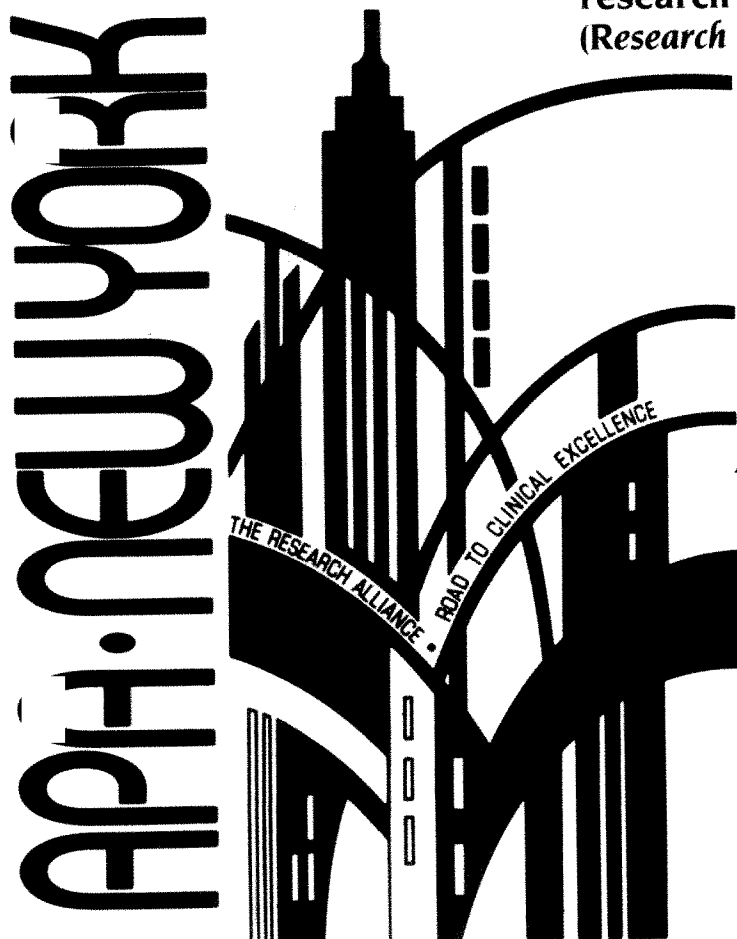
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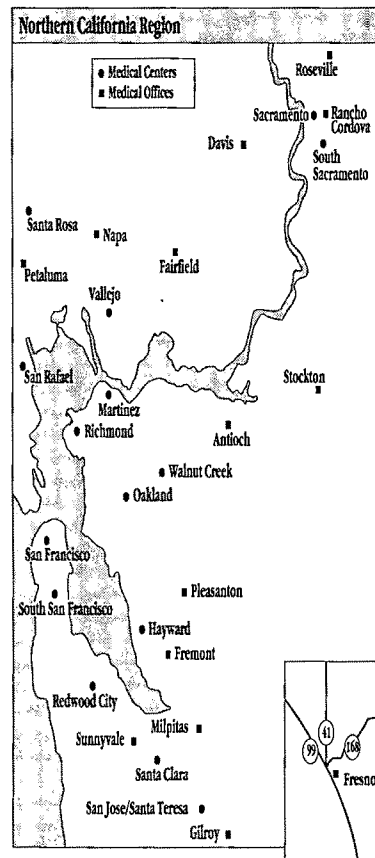
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**Contraindications:** Since the pharmacologic and clinical actions of HALDOL Decanoate 50 and HALDOL Decanoate 100 are attributed to HALDOL haloperidol as the active medication. Contraindications, Warnings, and additional information are those of HALDOL, modified to reflect the prolonged action.

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

**Warnings: Tardive Dyskinesia** Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

**Neuroleptic Malignant Syndrome (NMS):** A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored since recurrences of NMS have been reported. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with HALDOL.

**Usage in Pregnancy:** (see PRECAUTIONS—Usage in Pregnancy) **Combined Use With Lithium:** (see PRECAUTIONS—Drug Interactions)

**General:** Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS—Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

**Precautions:** Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur, metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold; if indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinson medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates, if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL.

The 1, 5, 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

**Information for Patients:** Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

**Drug Interactions:** Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear. As with other antipsychotic agents, it should be noted that HALDOL may be capable of potentiating CNS depressants such as anesthetics, opiates, and alcohol.

**Carcinogenesis, Mutagenesis and Impairment of Fertility:** No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsomal activation assay.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol-related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence, at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels, the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

**Usage in Pregnancy:** Pregnancy Category C. Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards to the fetus.

**Nursing Mothers:** Infants should not be nursed during drug treatment.

**Pediatric Use:** Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

**Adverse Reactions:** Adverse reactions following the administration of HALDOL Decanoate 50 or HALDOL Decanoate 100 are those of HALDOL haloperidol. Since vast experience has accumulated with HALDOL, the adverse reactions are reported for that compound as well as for haloperidol decanoate. As with all injectable medications, local tissue reactions have been reported with haloperidol decanoate.

**CNS Effects: Extrapyramidal Reactions**—Neuromuscular (extrapyramidal) reactions have been reported frequently often during the first few days of treatment. Generally they involved Parkinson-like symptoms which when first observed were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases. **Withdrawal Emergent Neurological Signs**—Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from Tardive Dyskinesia, except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available HALDOL should be gradually withdrawn. **Tardive Dyskinesia**—As with all antipsychotic agents HALDOL has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients irreversible. The syndrome is characterized by rhythmic involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk. There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked. It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop. **Tardive Dystonia**—Tardive dystonia, not associated with the above syndrome, has also been reported. Tardive dystonia is characterized by delayed onset of choreic or dystonic movements, is often persistent, and has the potential of becoming irreversible. **Other CNS Effects**—Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

**Body as a Whole:** Neuroleptic malignant syndrome (NMS), hyperpyrexia and heat stroke have been reported with HALDOL. (See WARNINGS for further information concerning NMS.) **Cardiovascular Effects:** Tachycardia, hypotension, hypertension and ECG changes. **Hematologic Effects:** Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis, agranulocytosis rarely reported and only in association with other medication. **Liver Effects:** Impaired liver function and/or jaundice. **Dermatologic Reactions:** Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. **Endocrine Disorders:** Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia. **Gastrointestinal Effects:** Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. **Autonomic Reactions:** Dry mouth, blurred vision, urinary retention, diaphoresis, and priapism. **Respiratory Effects:** Laryngospasm, bronchospasm and increased depth of respiration. **Special Senses:** Cataracts, retinopathy and visual disturbances. **Other:** Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

**IMPORTANT: Full directions for use should be read before HALDOL or HALDOL Decanoate products are administered or prescribed.**

**For information on symptoms and treatment of overdosage, see full prescribing information.**

The short-acting HALDOL injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

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During dose adjustment or episodes of exacerbation of psychotic symptoms, therapy with HALDOL Decanoate 100 or HALDOL Decanoate 50 can be supplemented with short-acting forms of HALDOL<sup>®</sup> (haloperidol). The side effects of the decanoate products are those of HALDOL. The prolonged action of HALDOL Decanoate 100 and HALDOL Decanoate 50 should be considered in the management of side effects.

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Volume 147, Number 5    May 1990

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## Brief Summary of Prescribing Information.

**Indications and Usage:** Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

**Contraindications:** Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

**Warnings:** Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

**Physical and Psychological Dependence:** Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

**Precautions:** In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any anxiolytic agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

**ESSENTIAL LABORATORY TESTS:** Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

**CLINICALLY SIGNIFICANT DRUG INTERACTIONS:** Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

**CARCINOGENESIS AND MUTAGENESIS:** No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

**PREGNANCY:** Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chloridiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

**NURSING MOTHERS:** It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

**Adverse Reactions,** if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.

**Overdosage:** In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levaterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

**DOSAGE:** Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.

**HOW SUPPLIED:** 0.5, 1.0 and 2.0mg tablets.



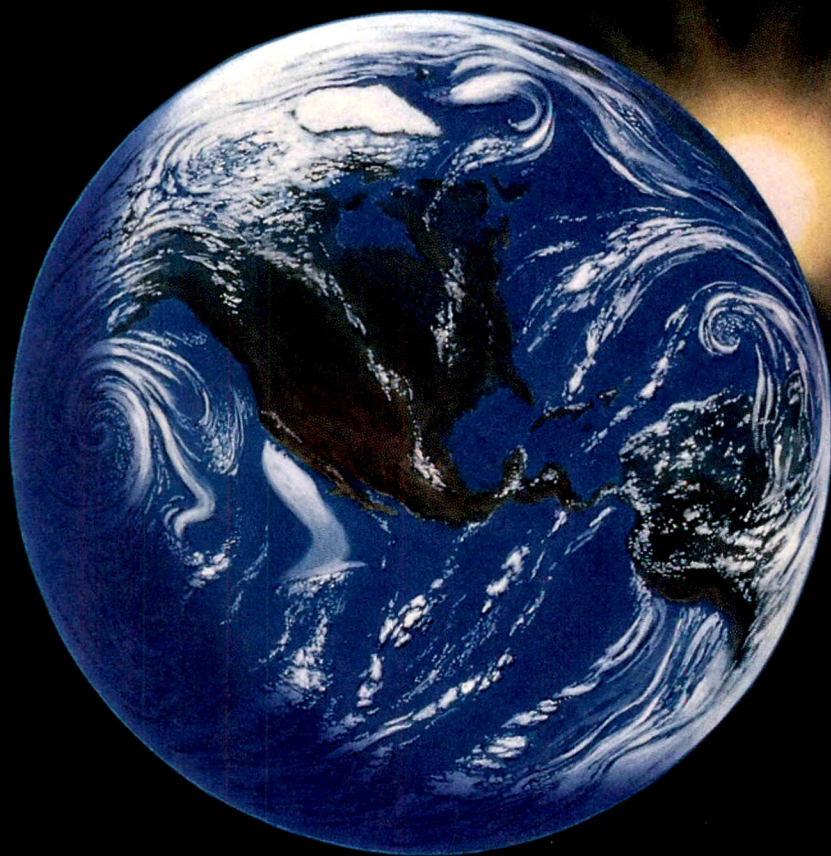
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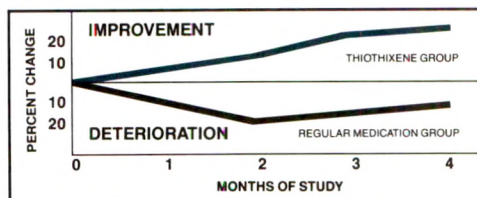


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(Adapted from DiMascio and Demigian<sup>2,3</sup>)

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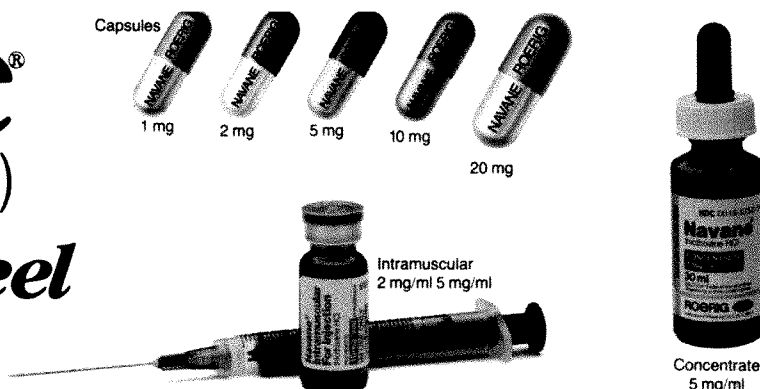
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**References:** 1. Bressler B, Friedel RO: A comparison between chlorpromazine and thiothixene in a Veterans Administration hospital population. *Psychosomatics* 1971;12:275-277. 2. DiMascio A, Demingir E: Study of the activating properties of thiothixene. *Psychosomatics* 1972;13:105-108. 3. DiMascio A, Demingir E: Job training in the rehabilitation of the chronic schizophrenic. Presented as a Scientific Exhibit at The American Psychiatric Association, Washington, DC, May 3-6, 1971. 4. Goldstein B, Weiner D, Banas F: Clinical evaluation of thiothixene in chronic ambulatory schizophrenic patients, in Lehmann HE, Ban TA (eds): *The Thioxanthenes: Modern Problems of Pharmacopsychiatry*. Basel, Switzerland, S. Karger, 1969, vol 2, pp 45-52. 5. Dillenkoff RL, Gallant DM, George RB, et al: Electrocardiographic evaluation of schizophrenic patients: A double-blind comparison. Presented as a Scientific Exhibit at The 125th Annual Meeting of the American Psychiatric Association, Dallas, May 1-4, 1972. 6. Data available on request from Roerig.

## BRIEF SUMMARY OF PRESCRIBING INFORMATION

**Navane® (thiothixene) Capsules:** 1 mg, 2 mg, 5 mg, 10 mg, 20 mg  
**(thiothixene hydrochloride) Concentrate:** 5 mg/ml, **Intramuscular:** 2 mg/ml, 5 mg/ml

**Indications:** Navane is effective in the management of manifestations of psychotic disorders. Navane has not been evaluated in the management of behavioral complications in patients with mental retardation.

**Contraindications:** Contraindicated in patients with circulatory collapse, comatose states, central nervous system depression due to any cause, and blood dyscrasias. Contraindicated in individuals who have shown hypersensitivity to the drug. It is not known whether there is a cross-sensitivity between the thioxanthenes and the phenothiazine derivatives, but the possibility should be considered.

**Warnings:** *Tardive Dyskinesia*—Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that: 1) is known to respond to neuroleptic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to Information for Patients in the Precautions section, and to the Adverse Reactions section.)

**Neuroleptic Malignant Syndrome (NMS)**—A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

**Usage in Pregnancy**—Safe use of Navane during pregnancy has not been established. Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus. Animal reproduction studies and clinical experience to date have not demonstrated any teratogenic effects.

In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents. After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen. (See Precautions.)

**Usage in Children**—The use of Navane in children under 12 years of age is not recommended because safety and efficacy in the pediatric age group have not been established.

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol.

**Precautions:** An antiemetic effect was observed in animal studies with Navane; since this effect may also occur in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumor.

In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold. Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered concurrently.

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with other CNS depressants other than anticonvulsant drugs.

Though exhibiting rather weak anticholinergic properties, Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving atropine or related drugs.

Use with caution in patients with cardiovascular disease.

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine lenticular pigmentation has been noted in a small number of patients treated with Navane for prolonged

periods). Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenic purpura), and liver damage (jaundice, biliary stasis) have been reported with related drugs.

Undue exposure to sunlight should be avoided. Photosensitive reactions have been reported in patients on Navane (thiothixene).

**Intramuscular Administration**—As with all intramuscular preparations, Navane Intramuscular should be injected well within the body of a relatively large muscle. The preferred sites are the upper outer quadrant of the buttock (i.e. gluteus maximus) and the mid-lateral thigh.

The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-thirds of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecostasia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

**Information for Patients**—Given the likelihood that some patients exposed chronically to neuroleptics will develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, if possible, full information about this risk. The decision to inform patients and/or their guardians must obviously take into account the clinical circumstances and the competency of the patient to understand the information provided.

**Adverse Reactions:** *Note:* Not all of the following adverse reactions have been reported with Navane (thiothixene). However, since Navane has certain chemical and pharmacologic similarities to the phenothiazines, all of the known side effects and toxicity associated with phenothiazine therapy should be borne in mind when Navane is used.

**Cardiovascular effects:** Tachycardia, hypotension, lightheadedness, and syncope. In the event hypotension occurs, epinephrine should not be used as a pressor agent since a paradoxical further lowering of blood pressure may result. Nonspecific EKG changes have been observed in some patients receiving Navane (thiothixene). These changes are usually reversible and frequently disappear on continued Navane therapy. The incidence of these changes is lower than that observed with some phenothiazines. The clinical significance of these changes is not known.

**CNS effects:** Drowsiness, usually mild, may occur although it usually subsides with continuation of Navane therapy. The incidence of sedation appears similar to that of the piperazine group of phenothiazines, but less than that of certain aliphatic phenothiazines. Restlessness, agitation and insomnia have been noted with Navane. Seizures and paradoxical exacerbation of psychotic symptoms have occurred with Navane infrequently.

Hyperreflexia has been reported in infants delivered from mothers having received structurally related drugs.

In addition, phenothiazine derivatives have been associated with cerebral edema and cerebrospinal fluid abnormalities.

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia, and dystonia have been reported. Management of these extrapyramidal symptoms depends upon the type and severity. Rapid relief of acute symptoms may require the use of an injectable antiparkinson agent. More slowly emerging symptoms may be managed by reducing the dosage of Navane and/or administering an oral antiparkinson agent.

**Persistent Tardive Dyskinesia:** As with all antipsychotic agents tardive dyskinesia may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The syndrome is characterized by rhythmic involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities.

Since early detection of tardive dyskinesia is important, patients should be monitored on an ongoing basis. It has been reported that fine vermicular movement of the tongue may be an early sign of the syndrome. If this or any other presentation of the syndrome is observed, the clinician should consider possible discontinuation of neuroleptic medication. (See Warnings section.)

**Hepatic Effects:** Elevations of serum transaminase and alkaline phosphatase, usually transient, have been infrequently observed in some patients. No clinically confirmed cases of jaundice attributable to Navane have been reported.

**Hematologic Effects:** As is true with certain other psychotropic drugs, leukopenia and leukocytosis, which are usually transient, can occur occasionally with Navane. Other antipsychotic drugs have been associated with agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopenia.

**Allergic Reactions:** Rash, pruritus, urticaria, photosensitivity and rare cases of anaphylaxis have been reported with Navane. Undue exposure to sunlight should be avoided. Although not experienced with Navane, exfoliative dermatitis and contact dermatitis (in nursing personnel) have been reported with certain phenothiazines.

**Endocrine Disorders:** Lactation, moderate breast enlargement and amenorrhea have occurred in a small percentage of females receiving Navane. If persistent, this may necessitate a reduction in dosage or the discontinuation of therapy. Phenothiazines have been associated with false positive pregnancy tests, gynecostasia, hypoglycemia, hyperglycemia, and glycosuria.

**Autonomic Effects:** Dry mouth, blurred vision, nasal congestion, constipation, increased sweating, increased salivation, and impotence have occurred infrequently with Navane therapy. Phenothiazines have been associated with miosis, mydriasis, and adynamic ileus.

**Other Adverse Reactions:** Hyperpyrexia, anorexia, nausea, vomiting, diarrhea, increase in appetite and weight, weakness or fatigue, polydipsia and peripheral edema.

Although not reported with Navane, evidence indicates there is a relationship between phenothiazine therapy and the occurrence of a systemic lupus erythematosus-like syndrome.

**Neuroleptic Malignant Syndrome (NMS):** Please refer to the text regarding NMS in the WARNINGS section.

**NOTE:** Sudden deaths have occasionally been reported in patients who have received certain phenothiazine derivatives. In some cases the cause of death was apparently cardiac arrest or asphyxia due to failure of the cough reflex. In others, the cause could not be determined nor could it be established that death was due to phenothiazine administration.

**Dosage:** Dosage of Navane should be individually adjusted depending on the chronicity and severity of the condition. See full prescribing information.

**Overdosage:** For information on signs and symptoms, and treatment of overdosage, see full prescribing information.

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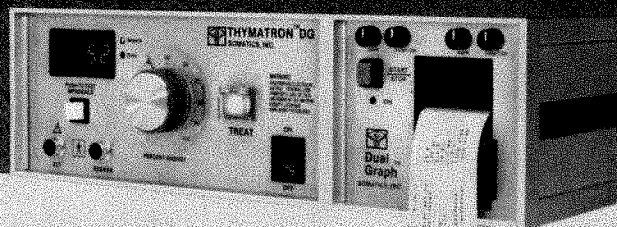
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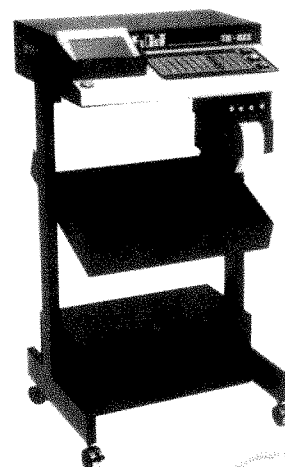
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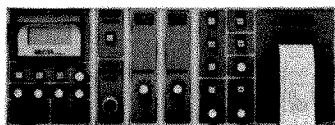
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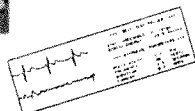
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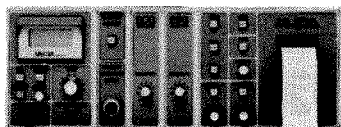
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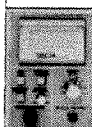
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## chlorpromazine

See complete prescribing information in SK&F literature or PDR. The following is a brief summary.

**Contraindications:** Comatose states or presence of large amounts of C.N.S. depressants.

**Warnings:** The possibility of extrapyramidal reactions from chlorpromazine may confuse the diagnosis of Reye's syndrome or other encephalopathy. Therefore, avoid use in children or adolescents with suspected Reye's syndrome.

May cause persistent tardive dyskinesia, which appears to be irreversible in some patients. Reserve chronic neuroleptic treatment for patients with chronic illness 1) that is known to respond to neuroleptics and 2) for whom there are no safer but equally effective treatment options. Use the smallest effective dose over the shortest treatment duration. If signs and symptoms of tardive dyskinesia develop, consider discontinuing the neuroleptic. A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. To manage NMS 1) discontinue immediately antipsychotic drugs and any other drugs not essential to concurrent therapy; 2) treat symptoms intensively and monitor; 3) where possible, treat serious concomitant medical problems. If antipsychotic treatment is needed after recovery from NMS, consider reintroducing drug therapy and monitor the patient carefully as recurrences of NMS have been reported. 'Thorazine' ampuls and vials contain sodium bisulfite and sodium sulfite; the sulfite may cause allergic reactions, including anaphylactic symptoms. In patients with bone marrow depression or previously demonstrated hypersensitivity (e.g., blood dyscrasias, jaundice) with phenothiazines, do not administer 'Thorazine' unless the potential treatment benefits outweigh the possible hazards. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery) especially during the first few days of therapy. Avoid concomitant use with alcohol. May counteract antihypertensive effect of guanethidine and related compounds. Use in pregnancy only when essential. There are reported instances of prolonged jaundice, extrapyramidal signs, hyperreflexia or hyporeflexia in newborns whose mothers had received chlorpromazine. Chlorpromazine is excreted in the breast milk of nursing mothers.

**Precautions:** Advise patients and/or guardians of the risk of tardive dyskinesia from chronic therapy. Use cautiously in persons with cardiovascular, liver, renal or chronic respiratory disease, or with acute respiratory infections. Patients with a history of hepatic encephalopathy due to cirrhosis have increased sensitivity to the C.N.S. effects of chlorpromazine. Due to cough reflex suppression, aspiration of vomitus is possible. May prolong or intensify the action of C.N.S. depressants, organophosphorus insecticides, heat, atropine and related drugs. (Reduce dosage of concomitant C.N.S. depressants.) Anticonvulsant action of barbiturates is not intensified.

Neuroleptic drugs cause elevated prolactin levels that persist during chronic administration. Since approximately one third of human breast cancers are prolactin-dependent *in vitro*, this elevation is of potential importance if neuroleptic drug administration is contemplated in a patient with a previously detected breast cancer. Neither clinical nor epidemiologic studies to date, however, have shown an association between the chronic administration of neuroleptic drugs and mammary tumorigenesis. Chromosomal aberrations in spermatocytes and abnormal sperm have been demonstrated in rodents treated with certain neuroleptics. Use cautiously in glaucoma patients. May diminish the effect of oral anticoagulants, produce  $\alpha$ -adrenergic blockade, and lower the convulsive threshold; dosage adjustment of anticonvulsants may be required. May interfere with Dilantin® metabolism, causing 'Dilantin' toxicity. May cause false positive phenylketonuria test results. Do not use with Ampaque®†. Discontinue 'Thorazine' at least 48 hours before myelography, do not resume for at least 24 hours postprocedure, and do not use to control N/V prior to myelography or postprocedure with 'Ampaque'. Evaluate patients with a history of long-term therapy with 'Thorazine' and/or other neuroleptics periodically to decide whether the dosage could be reduced or therapy discontinued. Antiemetic effect may mask signs of overdosage of other drugs or obscure diagnosis and treatment of conditions such as intestinal obstruction, brain tumor and Reye's syndrome (see Warnings). When used concomitantly, may obscure vomiting as a sign of toxicity of a cancer chemotherapeutic agent. Discontinue high-dose, long-term therapy gradually. Patients with a history of long-term therapy with 'Thorazine' and/or other neuroleptics should be evaluated periodically for possible adjustment or discontinuance of drug therapy.

**Adverse Reactions:** Drowsiness; cholestatic jaundice; agranulocytosis, eosinophilia, leukopenia, hemolytic anemia, aplastic anemia, thrombocytopenic purpura and pancytopenia; postural hypotension, tachycardia, fainting, dizziness and occasionally a shock-like condition; reversal of epinephrine effects; EKG changes have been reported; neuromuscular (extrapyramidal) reactions: dystonias, motor restlessness, pseudo-parkinsonism, persistent tardive dyskinesia, psychotic symptoms, catatonic-like states, cerebral edema; convulsive seizures; abnormality of the cerebrospinal fluid proteins; urticarial reactions and photosensitivity, exfoliative dermatitis, contact dermatitis; asthma, laryngeal edema, angioneurotic edema, and anaphylactoid reactions; lactation and breast engorgement (in females on large doses), false positive pregnancy tests, amenorrhea, gynecomastia; hyperglycemia, hypoglycemia, glycosuria; dry mouth, nasal congestion, constipation, adynamic ileus, urinary retention, priapism, miosis, mydriasis; after prolonged substantial doses, skin pigmentation, epithelial keratopathy, lenticular and corneal deposits and pigmentary retinopathy, visual impairment; mild fever (after large I.M. doses); hyperpyrexia; increased appetite and weight; a systemic lupus erythematosus-like syndrome; peripheral edema.

NOTE: Sudden death in patients taking phenothiazines (apparently due to cardiac arrest or asphyxia due to failure of cough reflex) has been reported but no causal relationship has been established.

**How Supplied: Tablets:** 10 mg, 25 mg or 50 mg, in bottles of 100 and 1000; in Single Unit Packages of 100 (intended for institutional use only). For use in severe neuropsychiatric conditions, 100 mg and 200 mg, in bottles of 100 and 1000; in Single Unit Packages of 100 (intended for institutional use only).

**Spansule® brand of sustained release capsules:** 30 mg, 75 mg, 150 mg or 200 mg, in bottles of 50 and 500; in Single Unit Packages of 100 (intended for institutional use only). For use in severe neuropsychiatric conditions, 300 mg, in bottles of 50; in Single Unit Packages of 100 (intended for institutional use only).

**Ampuls:** 1 mL and 2 mL (25 mg/mL), in boxes of 10, 100 and 500.

**Multiple-dose Vials:** 10 mL (25 mg/mL), in boxes of 1, 20 and 100.

**Syrup:** 10 mg/5 mL in 4 fl oz bottles.

**Suppositories:** 25 mg or 100 mg, in boxes of 12.

**Concentrate:** Intended for institutional use, 30 mg/mL, in 4 fl oz bottles and in cartons of 36 bottles. 100 mg/mL, in 8 fl oz bottles, in cartons of 12.

\*phenytoin, Parke-Davis.

†metrizamide, Winthrop Pharmaceuticals.

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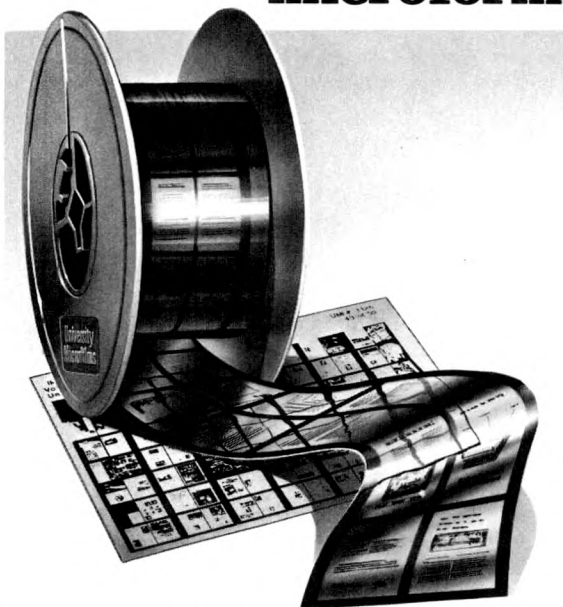
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\*The 150-mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.

Please see brief summary of SINEQUAN® (doxepin HCl) prescribing information on next page.

**References:** 1. Goldberg HL: Sleep disturbance as a manifestation of depression, in *Somatic Depression: Insights for Primary Care Physicians*. Proceedings of a symposium held in Miami, Dec 4, 1978. New York. Postgraduate Medicine Communications, pp 13-18. 2. Karacan I, Blackburn AB, Thornby JI, et al: The effect of doxepin HCl (Sinequan) on sleep patterns and clinical symptomatology of neurotic depressed patients with sleep disturbance, in *Sinequan® (doxepin HCl): A Monograph of Recent Clinical Studies*. Princeton, NJ. Excerpta Medica, 1977, pp 4-22. 3. Goldberg HL, Finnerty RJ: The use of doxepin in the treatment of symptoms of anxiety neurosis and accompanying depression: A collaborative controlled study. *Am J Psychiatry* 1972;129(July):74-77.

# SINEQUAN® (doxepin HCl)

## BRIEF SUMMARY

### SINEQUAN® (doxepin HCl) Capsules/Oral Concentrate

**Contraindications:** SINEQUAN is contraindicated in individuals who have shown hypersensitivity to the drug. Possibility of cross sensitivity with other dibenzoxepines should be kept in mind.

**SINEQUAN** is contraindicated in patients with glaucoma or a tendency to urinary retention. These disorders should be ruled out, particularly in older patients.

**Warnings:** The once-a-day dosage regimen of SINEQUAN in patients with intercurrent illness or patients taking other medications should be carefully adjusted. This is especially important in patients receiving other medications with anticholinergic effects.

**Usage in Geriatrics:** The use of SINEQUAN on a once-a-day dosage regimen in geriatric patients should be adjusted carefully based on the patient's condition.

**Usage in Pregnancy:** Reproduction studies have been performed in rats, rabbits, monkeys and dogs and there was no evidence of harm to the animal fetus. The relevance to humans is not known. Since there is no experience in pregnant women who have received this drug, safety in pregnancy has not been established. There has been a report of apnea and drowsiness occurring in a nursing infant whose mother was taking SINEQUAN.

**Usage in Children:** The use of SINEQUAN in children under 12 years of age is not recommended because safe conditions for its use have not been established.

### Drug Interactions

**MAO Inhibitors:** Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least two weeks prior to the cautious initiation of therapy with SINEQUAN. The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

**Cimetidine:** Cimetidine has been reported to produce clinically significant fluctuations in steady-state serum concentrations of various tricyclic antidepressants. Serious anticholinergic symptoms (i.e., severe dry mouth, urinary retention and blurred vision) have been associated with elevations in the serum levels of tricyclic antidepressant when cimetidine therapy is initiated. Additionally, higher than expected tricyclic antidepressant levels have been observed when they are begun in patients already taking cimetidine. In patients who have been reported to be well controlled on tricyclic antidepressants receiving concurrent cimetidine therapy, discontinuation of cimetidine has been reported to decrease established steady-state serum tricyclic antidepressant levels and compromise their therapeutic effects.

**Alcohol:** It should be borne in mind that alcohol ingestion may increase the danger inherent in any intentional or unintentional SINEQUAN overdose. This is especially important in patients who may use alcohol excessively.

**Tolazamide:** A case of severe hypoglycemia has been reported in a type II diabetic patient maintained on tolazamide (1 gm/day) 11 days after the addition of doxepin (75 mg/day).

**Precautions:** Since drowsiness may occur with the use of this drug, patients should be warned of the possibility and cautioned against driving a car or operating dangerous machinery while taking the drug. Patients should also be cautioned that their response to alcohol may be potentiated.

Since suicide is an inherent risk in any depressed patient and may remain so until significant improvement has occurred, patients should be closely supervised during the early course of therapy. Prescriptions should be written for the smallest feasible amount.

Should increased symptoms of psychosis or shift to manic symptomatology occur, it may be necessary to reduce dosage or add a major tranquilizer to the dosage regimen.

**Adverse Reactions:** NOTE: Some of the adverse reactions noted below have not been specifically reported with SINEQUAN use. However, due to the close pharmacological similarities among the tricyclics, the reactions should be considered when prescribing SINEQUAN (doxepin HCl).

**Anticholinergic Effects:** Dry mouth, blurred vision, constipation, and urinary retention have been reported. If they do not subside with continued therapy, or become severe, it may be necessary to reduce the dosage.

**Central Nervous System Effects:** Drowsiness is the most commonly noticed side effect. This tends to disappear as therapy is continued. Other infrequently reported CNS side effects are confusion, disorientation, hallucinations, numbness, paresthesias, ataxia, extrapyramidal symptoms, seizures, tardive dyskinesia, and tremor.

**Cardiovascular:** Cardiovascular effects including hypotension, hypertension, and tachycardia have been reported occasionally.

**Allergic:** Skin rash, edema, photosensitization, and pruritus have occasionally occurred.

**Hematologic:** Eosinophilia has been reported in a few patients. There have been occasional reports of bone marrow depression manifesting as agranulocytosis, leukopenia, thrombocytopenia, and purpura.

**Gastrointestinal:** Nausea, vomiting, indigestion, taste disturbances, diarrhea, anorexia, and aphthous stomatitis have been reported. (See anticholinergic effects.)

**Endocrine:** Raised or lowered libido, testicular swelling, gynecomastia in males, enlargement of breasts and galactorrhea in the female, raising or lowering of blood sugar levels, and syndrome of inappropriate antidiuretic hormone secretion have been reported with tricyclic administration.

**Other:** Dizziness, tinnitus, weight gain, sweating, chills, fatigue, weakness, flushing, jaundice, alopecia, headache, exacerbation of asthma, and hyperpyrexia (in association with chlorpromazine) have been occasionally observed as adverse effects.

**Withdrawal Symptoms:** The possibility of development of withdrawal symptoms upon abrupt cessation of treatment after prolonged SINEQUAN administration should be borne in mind. These are not indicative of addiction and gradual withdrawal of medication should not cause these symptoms.

**Dosage and Administration:** For most patients with illness of mild to moderate severity, a starting daily dose of 75 mg is recommended. Dosage may subsequently be increased or decreased at appropriate intervals and according to individual response. The usual optimum dose range is 75 mg/day to 150 mg/day.

In more severely ill patients higher doses may be required with subsequent gradual increase to 300 mg/day if necessary. Additional therapeutic effect is rarely to be obtained by exceeding a dose of 300 mg/day.

In patients with very mild symptomatology or emotional symptoms accompanying organic disease, lower doses may suffice. Some of these patients have been controlled on doses as low as 25-50 mg/day.

The total daily dosage of SINEQUAN may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed the maximum recommended dose is 150 mg/day. This dose may be given at bedtime. The 150 mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.

Anti-anxiety effect is apparent before the antidepressant effect. Optimal antidepressant effect may not be evident for two to three weeks.

### Overdosage

#### A. Signs and Symptoms

1. Mild: Drowsiness, stupor, blurred vision, excessive dryness of mouth.
2. Severe: Respiratory depression, hypotension, coma, convulsions, cardiac arrhythmias and tachycardias.

Also: urinary retention (bladder atony), decreased gastrointestinal motility (paralytic ileus), hyperthermia (or hypothermia), hypertension, dilated pupils, hyperactive reflexes.

#### B. Management and Treatment

1. Mild: Observation and supportive therapy is all that is usually necessary.
2. Severe: Medical management of severe SINEQUAN overdose consists of aggressive supportive therapy. If the patient is conscious, gastric lavage, with appropriate precautions to prevent pulmonary aspiration, should be performed even though SINEQUAN is rapidly absorbed. The use of activated charcoal has been recommended, as has been continuous gastric lavage with saline for 24 hours or more. An adequate airway should be established in comatose patients and assisted ventilation used if necessary. EKG monitoring may be required for several days, since relapse after apparent recovery has been reported. Arrhythmias should be treated with the appropriate antiarrhythmic agent. It has been reported that many of the cardiovascular and CNS symptoms of tricyclic antidepressant poisoning in adults may be reversed by the slow intravenous administration of 1 mg to 3 mg of physostigmine salicylate. Because physostigmine is rapidly metabolized, the dosage should be repeated as required. Convulsions may respond to standard anticonvulsant therapy, however, barbiturates may potentiate any respiratory depression. Dialysis and forced diuresis generally are not of value in the management of overdosage due to high tissue and protein binding of SINEQUAN.

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## VALIUM® (diazepam/Roche) (C)

Before prescribing, please consult complete product information, a summary of which follows:

**INDICATIONS:** Management of anxiety disorders, or short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not as sole therapy).

The effectiveness of Valium in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

**CONTRAINDICATED:** Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

**WARNINGS:** Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants.

**Usage in Pregnancy:** Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).

**PRECAUTIONS:** If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is

## VALIUM® (diazepam/Roche)

unclear. Inform patients to consult physician before increasing dose or abruptly discontinuing diazepam.

**SIDE EFFECTS:** Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

**Drug Abuse and Dependence:** Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuation of diazepam; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. After extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

**DOSAGE:** Individualize for maximum beneficial effect. **Adults:**

Anxiety disorders, symptoms of anxiety, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. **Geriatric or debilitated patients:** 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated.

(See Precautions.) **Children:** 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

**HOW SUPPLIED:** For oral administration, round, scored tablets with a cut out "V" design—2 mg, white; 5 mg, yellow; 10 mg, blue—bottles of 100 and 500.

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Yes. (202) 682-6057 is the number to call to request a computer literature search. Because search requests require a signed form, it's a good idea to keep a supply on hand. Call and ask us to send some for your next project. Charges for members are cost plus

\$15; non-members, cost plus \$40. Turnaround time is 2 weeks. Records retrieved include full bibliographic citations and in most cases abstracts.

### Can you help me find an article in *Psychiatric News*?

Yes. Call (202) 682-6080. The APA Library provides the only in-depth indexing service for *Psychiatric News*. There is complete coverage since 1978.



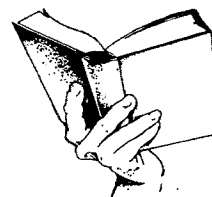
### Does the Library have audiovisual material? What kinds?

Yes. The Marion E. Kenworthy Learning Center's collection includes audiocassettes and videocassettes. The audio collection has taped symposia from annual meetings since 1976; the video collection has clinical presentations useful for staff and continuing medical education. The loan period is 2 weeks. Please call for charges.



### What's in the Archives?

The Archives holds the records created by the APA, such as minutes, reports, correspondence, and photographs. There are a few collections of papers of individual psychiatrists such as Daniel Blain, Leo Kanner and John C. Whitehorn. Additionally, the Archives is the sole repository for the papers of Albert Deutch. There are tapes and transcripts from an oral history project, and a collection of artifacts and photographs that relate to the history of American psychiatry. These materials may be used in the Archives or photocopied, but they do not circulate.



### Does the Library have a rare book collection?

Yes. Our rare book collection contains many valuable and first editions of early works that reflect the history of psychiatry. Among its volumes are first edition copies of Benjamin Rush's *Medical Inquiries and Observations Upon the Diseases of the Mind* and Joseph Breuer and Sigmund Freud's *Studien uber Hysterie*.

The growth of this collection depends on gifts. However, the Library is not authorized to give appraisals for income tax purposes.

### Would you like me to donate my books and old journals to the Library?

Yes. We are always pleased to receive gifts, but we must reserve the right to evaluate your gift for relevance to the Association and dispose of any books or journals we cannot use. Each donor is appropriately acknowledged on a bookplate attached to the volume.

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Absolutely! In fact the APA Library began in 1961 with a collection of autographed books by member-authors. This is a tradition we especially like to keep alive.

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# Introducing **HALDOL® Decanoate 100** (HALOPERIDOL) INJECTION

## Less volume per injection can enhance patient acceptance

New 100 mg/mL formulation is twice the concentration  
of the original 50 mg/mL decanoate formulation

- For many patients, fewer injections per dose may reduce anxiety and enhance patient compliance
- Multi-dose vial packaging means convenience for you and your staff



Please see brief summary of Prescribing Information on next page.

During dose adjustment or episodes of exacerbation of psychotic symptoms, therapy with HALDOL Decanoate 100 or HALDOL Decanoate 50 can be supplemented with short-acting forms of HALDOL® (haloperidol). The side effects of the decanoate products are those of HALDOL. The prolonged action of HALDOL Decanoate 100 and HALDOL Decanoate 50 should be considered in the management of side effects.

**McNEIL  
PHARMACEUTICAL**  
McNEILAB, INC., Spring House, PA 15177

**HALDOL® Decanoate 100**  
(HALOPERIDOL) INJECTION 100mg/mL  
**HALDOL® Decanoate 50**  
(HALOPERIDOL) INJECTION 50mg/mL

# HALDOL® Decanoate 100

(HALOPERIDOL) INJECTION 100mg/mL

# HALDOL® Decanoate 50

(HALOPERIDOL) INJECTION 50mg/mL

For IM Injection Only

The following is a brief summary only. Before prescribing, see complete prescribing information in HALDOL and HALDOL Decanoate product labeling.

**Contraindications:** Since the pharmacologic and clinical actions of HALDOL Decanoate 50 and HALDOL Decanoate 100 are attributed to HALDOL haloperidol as the active medication, Contraindications, Warnings, and additional information are those of HALDOL, modified to reflect the prolonged action.

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

**Warnings: Tardive Dyskinesia:** Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

**Neuroleptic Malignant Syndrome (NMS):** A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with HALDOL.

**Usage in Pregnancy:** (see PRECAUTIONS—Usage in Pregnancy) **Combined Use With Lithium:** (see PRECAUTIONS—Drug Interactions)

**General:** Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS—Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

**Precautions:** Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinson medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL.

The 1, 5, 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

**Information for Patients:** Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

**Drug Interactions:** Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear. As with other antipsychotic agents, it should be noted that HALDOL may be capable of potentiating CNS depressants such as anesthetics, opiates, and alcohol.

**Carcinogenesis, Mutagenesis and Impairment of Fertility:** No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsomal activation assay.

**Carcinogenicity studies** using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

**Usage in Pregnancy:** Pregnancy Category C. Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards to the fetus.

**Nursing Mothers:** Infants should not be nursed during drug treatment.

**Pediatric Use:** Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

**Adverse Reactions:** Adverse reactions following the administration of HALDOL Decanoate 50 or HALDOL Decanoate 100 are those of HALDOL haloperidol. Since vast experience has accumulated with HALDOL, the adverse reactions are reported for that compound as well as for haloperidol decanoate. As with all injectable medications, local tissue reactions have been reported with haloperidol decanoate.

**CNS Effects: Extrapyramidal Reactions—**Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which when first observed were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases. **Withdrawal Emergent Neurological Signs—**Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Tardive Dyskinesia," except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available HALDOL should be gradually withdrawn. **Tardive Dyskinesia—**As with all antipsychotic agents HALDOL has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients irreversible. The syndrome is characterized by rhythmic involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk. There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked. It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop. **Tardive Dystonia—**Tardive dystonia, not associated with the above syndrome, has also been reported. Tardive dystonia is characterized by delayed onset of choreic or dystonic movements, is often persistent, and has the potential of becoming irreversible. **Other CNS Effects—**Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

**Body as a Whole:** Neuroleptic malignant syndrome (NMS), hyperpyrexia and heat stroke have been reported with HALDOL. (See WARNINGS for further information concerning NMS.) **Cardiovascular Effects:** Tachycardia, hypotension, hypertension and ECG changes. **Hematologic Effects:** Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication. **Liver Effects:** Impaired liver function and/or jaundice. **Dermatologic Reactions:** Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. **Endocrine Disorders:** Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia and hypoparathyremia. **Gastrointestinal Effects:** Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. **Autonomic Reactions:** Dry mouth, blurred vision, urinary retention, diaphoresis, and priapism. **Respiratory Effects:** Laryngospasm, bronchospasm and increased depth of respiration. **Special Senses:** Cataracts, retinopathy and visual disturbances. **Other:** Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

**IMPORTANT: Full directions for use should be read before HALDOL or HALDOL Decanoate products are administered or prescribed. For information on symptoms and treatment of overdosage, see full prescribing information.**

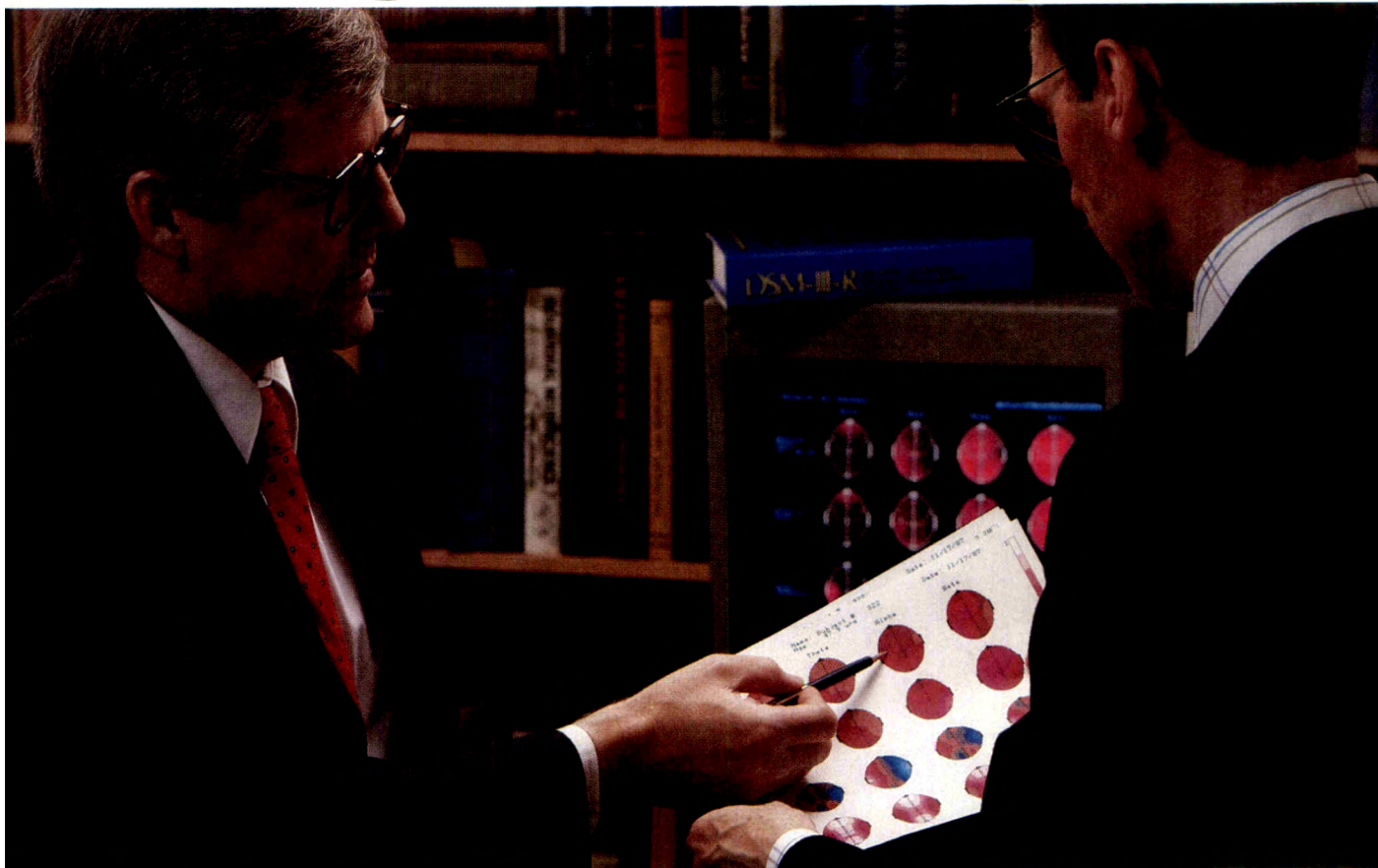
The short-acting HALDOL injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

McNeil Pharmaceutical, McNEILAB, INC., Spring House, PA 19477

8/23/89



# Diagnostic Edge.



## The Cadwell Spectrum 32. More objectivity in psychiatric diagnoses.

As new technologies provide more insight into brain function, psychiatry is integrating more objective data into diagnosis. The Cadwell Spectrum 32 Neurometric Analyzer provides the most comprehensive evaluation of brain electrical activity available. And gives you the diagnostic edge in corroborating a number of psychiatric disorders.

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## Calendar

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*For free listing of your organization's official annual or regional meeting, please send us the following information: sponsor, location, inclusive dates, type and number of continuing education credits (if available), and the name, address, and telephone number of the person or group to contact for more information. All notices and changes must be received no later than 120 days before the first day of the month of desired publication and should be addressed to Calendar, American Journal of Psychiatry, 1400 K St., N.W., Washington, DC 20005. Because of space limitations, only listings of meetings of the greatest interest to Journal readers will be included.*

### JULY

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July 2–7, 6th Prague International Conference on Psychological Development and Personality Formative Processes, Prague. Contact The 6th Prague International Conference, Institute of Psychology, Husova 4, 110 00 Prague 1, Czechoslovakia.

July 4–8, 2nd International Conference on The Future of Adult Life, Leeuwenhorst Congress Centre, The Netherlands. Contact Mike Featherstone, Centre for the Study of Adult Life, Department of Administrative and Social Studies, Teesside Polytechnic, Middlesbrough, Cleveland TS1 3BA, United Kingdom; (0642) 218121, ext. 4313.

July 5–7, 1st International Conference on Psychology and Performing Arts, London. Contact Dr. Glenn Wilson, Institute of Psychiatry, London SE5 8AF, United Kingdom; (01) 703-5411, ext. 3254.

July 11–14, 14th Annual Update in Neuroscience, Virginia Beach, Virginia. Contact Diana Martin-Williams; 804-230-1311.

July 16–20, 10th International Congress, International Association for Cross-Cultural Psychology, Nara, Japan. Contact Saburo Iwawaki, Graduate School of Education, Hyogo Kyoiku Diagaku, Yashirocho Katogun Hyogo, 673 Japan.

July 16–20, 12th International Congress of Child Psychiatry, International Association for Child and Adolescent Psychiatry and Allied Professions, Kyoto, Japan. Contact Professor Kosuke Yamazaki, c/o Dr. Reimer Jensen, Borups, alle 179, 2400 Copenhagen NV, Denmark.

July 18–22, annual meeting, National Alliance for the Mentally Ill, Chicago. Contact Laurie M. Flynn, 2101 Wilson Boulevard, Suite 302, Arlington, VA 22201; 703-524-9094.

July 19–22, annual meeting, Autism Society of America, Seattle. Contact Thomas Nerney, 1234 Massachusetts Avenue, NW, Suite C1017, Washington, DC 20005; 202-783-0125.

July 23–27, annual meeting, International Transactional Analysis Association, Brussels. Contact Susan Sevilla, 1772 Vallejo Street, San Francisco, CA 94123; 415-885-5992.

July 24–28, 24th CIOMS Conference on "Genetics, Ethics and Human Values: Humane Genome, Mapping, Screening & Treatment," Tokyo. Contact Multinational Meetings In-

formation Services, P.O. Box 5090, NL-1007 AB Amsterdam, The Netherlands; 3120/684451.

July 31–August 5, 2nd Congress on Human Rights, Medicine and Law, Bophuthatswana. Contact International Centre of Medicine & Law, University of Bophuthatswana, P.O. Box 4182, Bophuthatswana, Southern Africa; 27 (0) 140 842470-1.

### AUGUST

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August 11–15, annual meeting, American Sociological Association, Washington, D.C. Contact William V. D'Antonio, 1722 N Street, NW, Washington, DC 20036; 202-833-3410.

August 11–15, 10th International Symposium for the Psychotherapy of Schizophrenia, Stockholm. Contact Johan Cullberg, Conference President, P.O. Box 6911, S-102 39 Stockholm, Sweden; 46 8 2330990.

August 15–17, 8th International Conference on Risk and Gambling, London. Contact Judy A. Cornelius, Conference Coordinator, Institute for the Study of Gambling and Commercial Gaming, College of Business Administration, Mail Stop No. 024, University of Nevada, Reno, NV 89557-0016; 702-784-1477.

August 18–24, 5th European Congress of Hypnosis in Psychotherapy and Psychosomatic Medicine, Konstanz. Contact Walter Bongartz, University of Konstanz, 750 Konstanz, Federal Republic of Germany.

August 20–23, 9th International Congress, Medical Informatics Europe 90, "Health Added Value," Glasgow. Contact Dr. J. Bryden, Consultant in Health Information, Greater Glasgow Health Board, Department of Public Health Medicine, McLeod Street, Glasgow G4 0RA, Scotland; 041 553 1833, ext. 222.

August 20–24, 21st Congress, International Society of Psychoneuroendocrinology, Buffalo. Contact Uriel Halbreich, M.D., Department of Psychiatry, State University of New York at Buffalo, 462 Grider Street (K-Annex), Buffalo, NY 14215; 716-898-5088.

*(Continued on page A36)*



**PAMELOR®** (nortriptyline HCl)**BRIEF SUMMARY.**

Please see package insert for full prescribing information.

**Contraindications:** 1) Concurrent use with a monoamine oxidase (MAO) inhibitor, since hyperpyretic crises, severe convulsions, and fatalities have occurred when similar tricyclic antidepressants were used in such combinations. MAO inhibitors should be discontinued for at least two weeks before treatment with Pamelor® (nortriptyline HCl) is started. 2) Hypersensitivity to Pamelor® (nortriptyline HCl), cross-sensitivity with other dibenzazepines is a possibility. 3) The acute recovery period after myocardial infarction.

**Warnings:** Give only under close supervision to patients with cardiovascular disease, because of the tendency of the drug to produce sinus tachycardia and to prolong conduction time; myocardial infarction, arrhythmia, and strokes have occurred. The antihypertensive action of guanethidine and similar agents may be blocked. Because of its anticholinergic activity, nortriptyline should be used with great caution in patients who have glaucoma or a history of urinary retention. Patients with a history of seizures should be followed closely, since nortriptyline is known to lower the convulsive threshold. Great care is required in hyperthyroid patients or those receiving thyroid medication, since cardiac arrhythmias may develop. Nortriptyline may impair the mental and/or physical abilities required for the performance of hazardous tasks, such as operating machinery or driving a car; therefore, the patient should be warned accordingly. Excessive consumption of alcohol may have a potentiating effect, which may lead to the danger of increased suicidal attempts or overdosage, especially in patients with histories of emotional disturbances or suicidal ideation.

The concomitant administration of quinidine and nortriptyline may result in a significantly longer plasma half-life, higher A.U.C., and lower clearance of nortriptyline.

**Use in Pregnancy:**—Safe use during pregnancy and lactation has not been established; therefore, in pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards.

**Use in Children:**—Not recommended for use in children, since safety and effectiveness in the pediatric age group have not been established.

**Precautions:** Use in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms; in overactive or agitated patients, increased anxiety and agitation may occur; in manic-depressive patients, symptoms of the manic phase may emerge. Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed patients. Troublesome patient hostility may be aroused. Epileptiform seizures may accompany administration. Close supervision and careful adjustment of dosage are required when used with other anticholinergic drugs and sympathomimetic drugs. Concurrent administration of cimetidine can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressant. Patients should be informed that the response to alcohol may be exaggerated. When essential, may be administered with electroconvulsive therapy, although the hazards may be increased. Discontinue the drug for several days, if possible, prior to elective surgery. The possibility of a suicidal attempt by a depressed patient remains after the initiation of treatment; in this regard, it is important that the least possible quantity of drug be dispensed at any given time. Both elevation and lowering of blood sugar levels have been reported. A case of significant hypoglycemia has been reported in a type II diabetic patient maintained on chlorpropamide (250 mg/day), after the addition of nortriptyline (125 mg/day).

**Adverse Reactions:** *Cardiovascular:*—Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke. *Psychiatric:*—Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia, panic, nightmares; hypomania; exacerbation of psychosis. *Neurologic:*—Numbness, tingling, paresthesias of extremities, incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures; alteration in EEG patterns; tinnitus. *Anticholinergic:*—Dry mouth and, rarely, associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract. *Allergic:*—Skin rash, peptic ulcers, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); edema (general or of face and tongue); drug fever. *Other:*—Jaundice (simulating obstructive); altered liver function; weight gain or loss; perspiration; flushing; urinary frequency; nocturia; drowsiness, dizziness, weakness, fatigue; headache; parotid swelling; alopecia. *Withdrawal Symptoms:*—Though these are not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

**Overdosage:** Toxic overdosage may result in confusion, restlessness, agitation, vomiting, hyperpyrexia, muscle rigidity, hyperactive reflexes, tachycardia. ECG evidence of impaired conduction, shock, congestive heart failure, stupor, coma, and CNS stimulation with convulsions followed by respiratory depression. Deaths have occurred with drugs of this class. No specific antidote is known; general supportive measures are indicated, with gastric lavage.

(PAM-219—9/1/89)

**SANDOZ PHARMACEUTICALS**  
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# Productive Days... Restful Nights and Pamelor® (nortriptyline HCl)



The Full-Time Antidepressant  
for patients whose symptoms include  
insomnia and anxiety



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(nortriptyline HCl)

CAPSULES: 10 mg, 25 mg, 50 mg, and 75 mg; SOLUTION: 10 mg/5 mL and alcohol 4%

*The active metabolite of amitriptyline*

## Cambridge University Press

### The Cambridge Examination for Mental Disorders of the Elderly (CAMDEX)

Sir Martin Roth, F.A. Huppert, E. Tym, and C.Q. Mountjoy

This package, consisting of complete interview and examination schedules, a booklet of test materials, score sheets, and a manual, comprises a standard assessment and diagnosis of senile dementia, including Alzheimer's disease and related mental disorders of the elderly. 1988 35161-8 Boxed Set \$95.00

### Health and Behaviour

Selected Perspectives

Edited by David A. Hamburg and Norman Sartorius

An array of international experts discuss aspects of health care, such as the sociology of health care in developing countries, the mental health aspects of general health care and the dangers to children through disease, malnutrition and other factors.

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### Children with Down Syndrome

A Developmental Perspective

Edited by Dante Cicchetti and Marjorie Beeghly

The underlying theme of this book is that children with Down syndrome, despite their constitutional anomalies and their additional medical problems, can be understood from a normative developmental framework.

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38667-5 Paper \$19.95

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"The book is quite amazing in that it attempts and succeeds in summarizing and synthesizing the vast knowledge base of the early intervention field."—Edward Zigler, Yale University (from the Foreword)

This book has been designed to serve as a key resource for those who are interested in young children with disabilities or developmental vulnerabilities, and their families.

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Ervin Staub

Staub looks at the psychological factors that influence one group's desire to harm another. He goes on to consider the behavior of perpetrators and bystanders in four historical situations: the Holocaust (his primary example), the genocide of Armenians in Turkey, and "autogenocide" in Cambodia, and the "disappearances" in Argentina.

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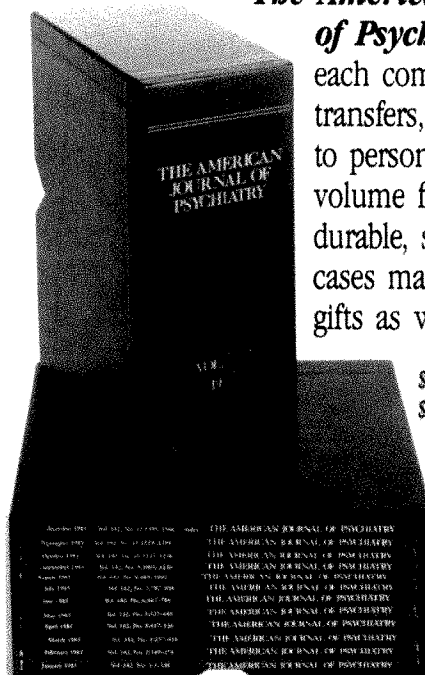
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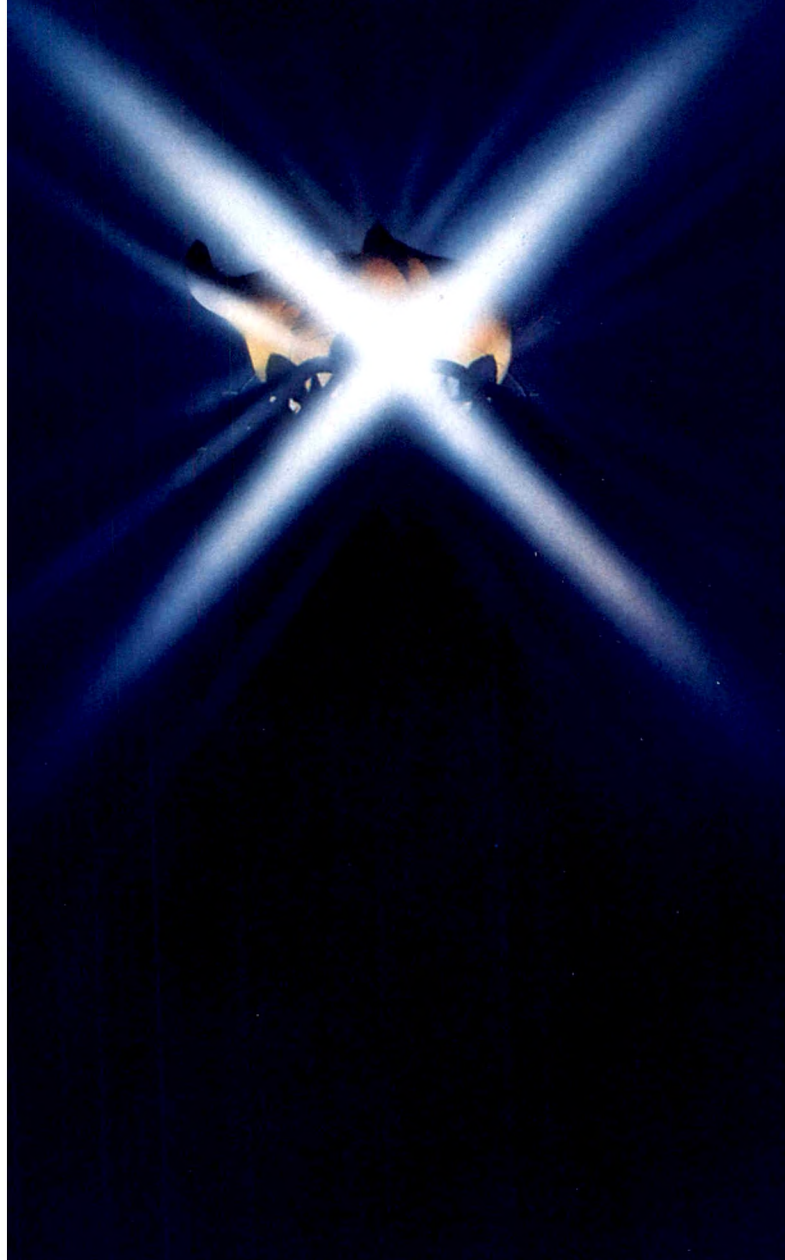
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‡Because of the substantial risk of seizure associated with CLOZARIL use, a dosage ceiling of 600 mg/day is recommended, although some patients may require up to 900 mg/day for a therapeutic effect.

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## CONTRAINDICATIONS

CLOZARIL is contraindicated in patients with myeloproliferative disorders, or a history of CLOZARIL-induced agranulocytosis or severe granulocytopenia. CLOZARIL should not be used simultaneously with other agents having a well-known potential to suppress bone marrow function. As with more typical antipsychotic drugs, CLOZARIL is contraindicated in severe central nervous system depression or comatose states from any cause.

## WARNINGS

### General

BECAUSE OF THE SIGNIFICANT RISK OF AGRANULOCYTOSIS, A POTENTIALLY LIFE-THREATENING ADVERSE EVENT (SEE BELOW), CLOZARIL SHOULD BE RESERVED FOR USE IN THE TREATMENT OF SEVERELY ILL SCHIZOPHRENIC PATIENTS WHO FAIL TO SHOW AN ACCEPTABLE RESPONSE TO ADEQUATE COURSES OF STANDARD ANTIPSYCHOTIC DRUG TREATMENT, EITHER BECAUSE OF INSUFFICIENT EFFECTIVENESS OR THE INABILITY TO ACHIEVE AN EFFECTIVE DOSE DUE TO INTOLERABLE ADVERSE EFFECTS FROM THOSE DRUGS. CONSEQUENTLY, BEFORE INITIATING TREATMENT WITH CLOZARIL, IT IS STRONGLY RECOMMENDED THAT A PATIENT BE GIVEN AT LEAST TWO TRIALS, EACH WITH A DIFFERENT STANDARD ANTIPSYCHOTIC DRUG PRODUCT, AT AN ADEQUATE DOSE AND FOR AN ADEQUATE DURATION.

PATIENTS WHO ARE BEING TREATED WITH CLOZARIL MUST HAVE A BASELINE WHITE BLOOD CELL (WBC) AND DIFFERENTIAL COUNT BEFORE INITIATION OF TREATMENT, AND A WBC COUNT EVERY WEEK THROUGHOUT TREATMENT, AND FOR FOUR WEEKS AFTER THE DISCONTINUATION OF CLOZARIL.

CLOZARIL IS AVAILABLE ONLY THROUGH THE CLOZARIL PATIENT MANAGEMENT SYSTEM<sup>SM</sup> (CPMS<sup>SM</sup>).

### Agranulocytosis

Agranulocytosis, defined as a granulocyte count (polys + bands) of less than 500 per mm<sup>3</sup>, has been estimated to occur in association with CLOZARIL use at a cumulative incidence at one year of approximately 1.3%, based on the occurrence of 15 U.S. cases out of 1743 patients exposed to CLOZARIL during its clinical testing prior to domestic marketing. All of these cases occurred at a time when the need for close monitoring of WBC counts was already recognized. This reaction could prove fatal if not detected early and therapy interrupted. While no fatalities have been associated with the U.S. agranulocytosis cases, and all cases have recovered fully, the U.S. sample is too small to reliably estimate the case fatality rate. Of the 112 cases of agranulocytosis reported worldwide in association with CLOZARIL use as of December 31, 1986, 35% were fatal. However, few of these deaths occurred since 1977, at which time the knowledge of CLOZARIL-induced agranulocytosis became more widespread, and close monitoring of WBC counts more widely practiced. Nevertheless, it is unknown at present what the case fatality rate will be for CLOZARIL-induced agranulocytosis, despite strict adherence to the recommendation for weekly monitoring of WBC counts.

Treatment should not be initiated if the WBC count is less than 3500 per mm<sup>3</sup>, or if the patient has a history of a myeloproliferative disorder, or previous CLOZARIL-induced agranulocytosis or granulocytopenia. Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat or any other signs of infection. If, after the initiation of treatment, the total WBC count has dropped below 3500 per mm<sup>3</sup> or it has dropped by a substantial amount from baseline, even if the count is above 3500 per mm<sup>3</sup>, or if immature forms are present, a repeat WBC count and a differential count should be done. If subsequent WBC counts and the differential count reveal a total WBC count between 3000 and 3500 per mm<sup>3</sup> and a granulocyte count above 1500 per mm<sup>3</sup>, twice weekly WBC counts and differential counts should be performed.

If the total WBC count falls below 3000 per mm<sup>3</sup> or the granulocyte count below 1500 per mm<sup>3</sup>, CLOZARIL therapy should be interrupted and patients should be carefully monitored for flu-like symptoms or other symptoms suggestive of infection. CLOZARIL therapy may be resumed if no symptoms of infection develop, and if the total WBC count returns to levels above 3000 per mm<sup>3</sup> and the granulocyte count returns to levels above 1500 per mm<sup>3</sup>. However, in this event, twice-weekly WBC counts and differential counts should continue until total WBC counts return to levels above 3500 per mm<sup>3</sup>.

If the total WBC count falls below 2000 per mm<sup>3</sup> or the granulocyte count falls below 1000 per mm<sup>3</sup>, bone marrow aspiration should be considered to ascertain granulopoietic status. Protective isolation with close observation may be indicated if granulopoiesis is determined to be deficient. Should evidence of infection develop, the patient should have appropriate cultures performed and an appropriate antibiotic regimen instituted.

Patients whose total WBC counts fall below 2000 per mm<sup>3</sup>, or granulocyte counts below 1000 per mm<sup>3</sup> during CLOZARIL therapy should *not* be re-challenged with CLOZARIL. Patients discontinued from CLOZARIL therapy due to significant WBC suppression have been found to develop agranulocytosis upon re-challenge, often with a shorter latency on re-exposure. To reduce the chances of re-challenge occurring in patients who have experienced significant bone marrow suppression during CLOZARIL therapy, a single, national master file will be maintained confidentially within the CPMS (Clozaril Patient Management System).

Except for evidence of significant bone marrow suppression during initial CLOZARIL therapy, there are no established risk factors, based on worldwide experience, for the development of agranulocytosis in association with CLOZARIL use. However, a disproportionate number of the U.S. cases of agranulocytosis occurred in patients of Jewish background compared to the overall proportion of such patients exposed during the domestic development of CLOZARIL. Most of the U.S. cases occurred within 4-10 weeks of exposure, but neither dose nor duration is a reliable predictor of this problem. No patient characteristics have been clearly linked to the development of agranulocytosis in association with CLOZARIL use, but agranulocytosis associated with other antipsychotic drugs has been reported to occur with a greater frequency in women, the elderly and in patients who are cachectic or have serious underlying medical illness; such patients may also be at particular risk with CLOZARIL.

To reduce the risk of agranulocytosis developing undetected, CLOZARIL will be dispensed only within the Clozaril Patient Management System.

## Seizures

Seizure has been estimated to occur in association with CLOZARIL use at a cumulative incidence at one year of approximately 5%, based on the occurrence of one or more seizures in 61 of 1743 patients exposed to CLOZARIL during its clinical testing prior to domestic marketing (i.e., a crude rate of 3.5%). Dose appears to be an important predictor of seizure, with a greater likelihood of seizure at the higher CLOZARIL doses used.

Caution should be used in administering CLOZARIL to patients having a history of seizures or other predisposing factors. Because of the substantial risk of seizure associated with CLOZARIL use, patients should be advised not to engage in any activity where sudden loss of consciousness could cause serious risk to themselves or others, e.g., the operation of complex machinery, driving an automobile, swimming, climbing, etc.

## Adverse Cardiovascular Effects

Orthostatic hypotension can occur with CLOZARIL treatment, especially during initial titration in association with rapid dose escalation, and may represent a continuing risk in some patients. Tachycardia, which may be sustained, has also been observed in approximately 25% of patients taking CLOZARIL, with patients having an average increase in pulse rate of 10-15 bpm. The sustained tachycardia is not simply a reflex response to hypotension, and is present in all positions monitored. Either tachycardia or hypotension may pose a serious risk for an individual with compromised cardiovascular function. A minority of CLOZARIL-treated patients experience ECG repolarization changes similar to those seen with other antipsychotic drugs, including S-T segment depression and flattening or inversion of T waves, which all normalize after discontinuation of CLOZARIL. The clinical significance of these changes is unclear. However, in clinical trials with CLOZARIL, several patients experienced significant cardiac events, including ischemic changes, myocardial infarction, nonfatal arrhythmias and sudden unexplained death. Causality assessment was difficult in many of these cases because of serious preexisting cardiac disease and plausible alternative causes. Rare instances of sudden, unexplained death have been reported in psychiatric patients, with or without associated antipsychotic drug treatment, and the relationship of these events to antipsychotic drug use is unknown. CLOZARIL should be used with caution in patients with known cardiovascular disease, and the recommendation for gradual titration of dose should be carefully observed.

## Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, a tared mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). No cases of NMS have been attributed to CLOZARIL alone. However, there have been several reported cases of NMS in patients treated concomitantly with lithium or other CNS-active agents.

## Tardive Dyskinesia

A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of treatment, which patients are likely to develop the syndrome.

There are several reasons for predicting that CLOZARIL may be different from other antipsychotic drugs in its potential for inducing tardive dyskinesia, including the preclinical finding that it has a relatively weak dopamine blocking effect and the clinical finding of a virtual absence of certain acute extrapyramidal symptoms, e.g., dystonia. In addition, there have been no confirmed cases of tardive dyskinesia developing in association with CLOZARIL use. Nevertheless, it cannot yet be concluded, without more extended experience, that CLOZARIL is incapable of inducing this syndrome.

## PRECAUTIONS

Because of the significant risk of agranulocytosis and seizure, both of which present a continuing risk over time, the extended treatment of patients failing to show an acceptable level of clinical response should ordinarily be avoided. In addition, the need for continuing treatment in patients exhibiting beneficial clinical responses should be periodically re-evaluated. During CLOZARIL therapy, patients may experience transient temperature elevations above 100.4°F (38°C), with the peak incidence within the first three weeks of treatment. While this fever is generally benign and self-limiting, it may necessitate discontinuing patients from treatment. On occasion, there may be an associated increase or decrease in WBC count. Patients with fever should be carefully evaluated to rule out the possibility of an underlying infectious process or the development of agranulocytosis. In the presence of high fever, the possibility of neuroleptic malignant syndrome (NMS) must be considered. CLOZARIL has very potent anticholinergic effects, and great care should be exercised in using this drug in the presence of prostatic enlargement or narrow angle glaucoma. Because of initial sedation, CLOZARIL may impair mental and/or physical abilities, especially during the first few days of therapy. The recommendations for gradual dose escalation should be carefully adhered to, and patients cautioned about activities requiring alertness. Clinical experience with CLOZARIL in patients with concomitant systemic diseases is limited. Nevertheless, caution is advisable in using CLOZARIL in patients with hepatic, renal or cardiac disease.

## Information for Patients

Patients who are to receive CLOZARIL should be warned about the significant risk of developing agranulocytosis. They should be informed that weekly blood tests are required to monitor for the occurrence of agranulocytosis, and that CLOZARIL tablets will be made available only through a special program designed to ensure the required blood monitoring. Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat, malaise, mucous membrane ulceration or other possible signs of infection. Particular attention should be paid to any flu-like complaints or other symptoms that might suggest infection. Patients should be informed of the significant risk of seizure during CLOZARIL treatment, and they should be advised to avoid driving and any other potentially hazardous activity while taking CLOZARIL. Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration. Patients should notify their physician if they are taking, or plan to take, any prescription or over-the-counter drugs or alcohol. Patients should notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should not breast feed an infant if they are taking CLOZARIL.

**CLOZARIL®**

(clozapine)

TABLETS

**Drug Interactions**

The risks of using CLOZARIL in combination with other drugs have not been systematically evaluated. The mechanism of CLOZARIL-induced agranulocytosis is unknown; nonetheless, the possibility that causative factors may interact synergistically to increase the risk and/or severity of bone marrow suppression warrants consideration. Therefore, CLOZARIL should not be used with other agents having a well-known potential to suppress bone marrow function. Given the primary CNS effects of CLOZARIL, caution is advised in using it concomitantly with other CNS-active drugs. Because CLOZARIL is highly bound to serum protein, the administration of CLOZARIL to a patient taking another drug which is highly bound to protein (e.g., warfarin, digoxin) may cause an increase in plasma concentrations of these drugs, potentially resulting in adverse effects. Conversely, adverse effects may result from displacement of protein-bound CLOZARIL by other highly bound drugs.

CLOZARIL may also potentiate the hypotensive effects of antihypertensive drugs and the anticholinergic effects of atropine-type drugs. The administration of epinephrine should be avoided in the treatment of drug-induced hypotension because of a possible reverse epinephrine effect.

**Pregnancy Category B**

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, and in view of the desirability of keeping the administration of all drugs to a minimum during pregnancy, this drug should be used only if clearly needed.

**ADVERSE REACTIONS**

Adverse events observed in association with the use of CLOZARIL in clinical trials at an incidence of 5% or greater were: central nervous system complaints, including drowsiness/sedation, dizziness/vertigo, headache and tremor; autonomic nervous system complaints, including salivation, sweating, dry mouth and visual disturbances; cardiovascular findings, including tachycardia, hypotension and syncope; and gastrointestinal complaints, including constipation and nausea; and fever. Complaints of drowsiness/sedation tend to subside with continued therapy or dose reduction. Salivation may be profuse, especially during sleep, but may be diminished with dose reduction.

**DOSAGE AND ADMINISTRATION****Initial Treatment**

It is recommended that treatment with CLOZARIL begin at 25 mg once or twice daily, and then be continued with daily dosage increments of 25 to 50 mg/day, if well-tolerated, to achieve a target dose of 300 to 450 mg/day by the end of two weeks. Subsequent dosage increments should be made no more than once- or twice-weekly, in increments not to exceed 100 mg. Cautious titration and a divided dosage schedule are necessary to minimize the risks of hypotension, seizure, and sedation.

**Therapeutic Dose Adjustment**

Daily dosing should continue on a divided basis as an effective and tolerable dose level is sought. While many patients may respond adequately at doses between 300-600 mg/day, it may be necessary to raise the dose to the 600-900 mg/day range to obtain an acceptable response. [Note: In the multicenter study providing the primary support for the superiority of CLOZARIL in treatment resistant patients, the mean and median CLOZARIL doses were both approximately 600 mg/day.]

Because of the possibility of increased adverse reactions at higher doses, particularly seizures, patients should ordinarily be given adequate time to respond to a given dose level before escalation to a higher dose is contemplated.

Dosing should not exceed 900 mg/day.

**Discontinuation of Treatment**

In the event of planned termination of CLOZARIL therapy, gradual reduction in dose is recommended over a 1 to 2 week period. However, should a patient's medical condition require abrupt discontinuation (e.g., leukopenia), the patient should be carefully observed for the recurrence of psychotic symptoms.

CLOZARIL is available only through the Clozaril Patient Management System, a program that combines white blood cell testing, patient monitoring, pharmacy, and drug distribution services, all linked to compliance with required safety monitoring.

To prescribe CLOZARIL call 1-800-237-CPMS (2767) or mail in a completed CPMS Enrollment Form.

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# In Tourette Syndrome

# ORAP™

## (pimozide) Tablets

## Helps Patients Be Themselves\*

### Excellent Symptom Control

Pimozide produced significantly more improvement of symptoms and less kinetic adverse effects than haloperidol. Improvement of 70% or more was reported by 74% of patients on pimozide compared with 45% on haloperidol ( $p < .02$ ), and 84% rated pimozide better overall than haloperidol."<sup>1</sup>

### Significantly Less Sedation than Haloperidol

In a double-blind, placebo-controlled study, "Pimozide was associated with lethargy or tiredness on significantly fewer days than haloperidol ( $p < .01$ ), and this was reflected in greater immediate and long-term patient acceptance...."<sup>2</sup>

### Documented Clinical Experience

Pimozide has been used in the treatment of Tourette Syndrome for over 10 years.<sup>1</sup>

For more information on ORAP, call  
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## The Less Sedating Therapy for Tourette Syndrome

P is indicated for patients who have failed to respond satisfactorily to standard treatment.  
see following page for a brief summary of prescribing information.

GATE Pharmaceuticals  
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# ORAP™ The Less Sedating Therapy for Tourette Syndrome

(pimozide) Tablets

## INDICATIONS AND USAGE

ORAP (pimozide) is indicated for the suppression of motor and phonic tics in patients with Tourette's Disorder who have failed to respond satisfactorily to standard treatment. ORAP is not intended as a treatment of first choice nor is it intended for the treatment for tics that are merely annoying or cosmetically troublesome. ORAP should be reserved for use in Tourette's Disorder patients whose development and/or daily life function is severely compromised by the presence of motor and phonic tics.

Evidence supporting approval of pimozide for use in Tourette's Disorder was obtained in two controlled clinical investigations which enrolled patients between the ages of 8 and 53 years. Most subjects in the two trials were 12 or older.

## CONTRAINDICATIONS

1. ORAP (pimozide) is contraindicated in the treatment of simple tics or tics other than associated with Tourette's Disorder.
2. ORAP should not be used in patients taking drugs that may, themselves, cause motor and phonic tics (e.g., pemoline, methylphenidate and amphetamines) and/or such patients have been withdrawn from these drugs to determine whether or not the drugs, rather than Tourette's Disorder, are responsible for the tics.
3. Because ORAP prolongs the QT interval of the electrocardiogram it is contraindicated in patients with congenital long QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs which prolong the QT interval of the electrocardiogram (see DRUG INTERACTIONS).
4. ORAP is contraindicated in patients with severe toxic central nervous system depression or comatose states from any cause.
5. ORAP is contraindicated in patients with hypersensitivity to it. As it is not known whether cross-sensitivity exists among the antipsychotics, pimozide should be used with appropriate caution in patients who have demonstrated hypersensitivity to other antipsychotic drugs.

## WARNINGS

The use of ORAP (pimozide) in the treatment of Tourette's Disorder involves different risk/benefit considerations than when antipsychotic drugs are used to treat other conditions. Consequently, a decision to use ORAP should take into consideration the following: (see also PRECAUTIONS—Information for Patients).

**Tardive Dyskinesia** A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to antipsychotic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS and PRECAUTIONS—Information for Patients.)

**Neuroleptic Malignant Syndrome (NMS)** A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperreflexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Hyperreflexia, not associated with the above symptom complex, has been reported with other antipsychotic drugs.

**Other** Sudden, unexpected deaths have occurred in experimental studies of conditions other than Tourette's Disorder. These deaths occurred while patients were receiving dosages in the range of 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. An electrocardiogram should be performed before ORAP treatment is initiated and periodically thereafter, especially during the period of dose adjustment.

ORAP may have a tumorigenic potential. Based on studies conducted in mice, it is known that pimozide can produce a dose related increase in pituitary tumors. The full significance of this finding is not known, but should be taken into consideration in the physician's and patient's decisions to use this drug product. This finding should be given special consideration when the patient is young and chronic use of pimozide is anticipated. (see PRECAUTIONS—Carcinogenesis, Mutagenesis, Impairment of Fertility).

## PRECAUTIONS

**General** ORAP (pimozide) may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery, especially during the first few days of therapy.

ORAP produces anticholinergic side effects and should be used with caution in individuals whose conditions may be aggravated by anticholinergic activity.

ORAP should be administered cautiously to patients with impairment of liver or kidney function, because it is metabolized by the liver and excreted by the kidneys.

Antipsychotics should be administered with caution to patients receiving anticonvulsant medication, with a history of seizures, or with EEG abnormalities, because they may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be maintained concomitantly.

**Laboratory Tests** An ECG should be done at baseline and periodically thereafter throughout the period of dose adjustment. Any indication of prolongation of QT<sub>c</sub> interval beyond an absolute limit of 0.47 seconds (children) or 0.52 seconds (adults), or more than 25% above the patient's original baseline should be considered a basis for stopping further dose increase (see CONTRAINDICATIONS) and considering a lower dose.

Since hypokalemia has been associated with ventricular arrhythmias, potassium insufficiency, secondary to diuretics, diarrhea, or other cause, should be corrected before ORAP therapy is initiated and normal potassium maintained during therapy.

**Drug Interactions** Because ORAP prolongs the QT interval of the electrocardiogram, an additive effect on QT interval would be anticipated if administered with other drugs, such

as phenothiazines, tricyclic antidepressants or antiarrhythmic agents, which prolong the QT interval. Such concomitant administration should not be undertaken (see CONTRAINDICATIONS).

ORAP may be capable of potentiating CNS depressants, including analgesics, sedatives, anxiolytics, and alcohol.

**Carcinogenesis, Mutagenesis, Impairment of Fertility** Carcinogenicity studies were conducted in mice and rats. In mice, pimozide causes a dose-related increase in pituitary and mammary tumors.

When mice were treated for up to 18 months with pimozide, pituitary gland changes developed in females only. These changes were characterized as hyperplasia at doses approximating the human dose and adenoma at doses about fifteen times the maximum recommended human dose on a mg per kg basis. The mechanism for the induction of pituitary tumors in mice is not known.

Mammary gland tumors in female mice were also increased, but these tumors are expected in rodents treated with antipsychotic drugs which elevate prolactin levels. Chronic administration of an antipsychotic also causes elevated prolactin levels in humans.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomasia, and impotence have been reported with antipsychotic drugs, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of these drugs and mammary tumorigenesis. The available evidence, however, is considered too limited to be conclusive at this time.

In a 24 month carcinogenicity study in rats, animals received up to 50 times the maximum recommended human dose. No increased incidence of overall tumors or tumors at any site was observed in either sex. Because of the limited number of animals surviving this study, the meaning of these results is unclear.

Pimozide did not have mutagenic activity in the Ames test with four bacterial test strains, in the mouse dominant lethal test or in the micronucleus test in rats.

Reproduction studies in animals were not adequate to assess all aspects of fertility. Nevertheless, female rats administered pimozide had prolonged estrus cycles, an effect also produced by other antipsychotic drugs.

**Pregnancy Category C.** Reproduction studies performed in rats and rabbits at oral doses up to 8 times the maximum human dose did not reveal evidence of teratogenicity. In the rat, however, this multiple of the human dose resulted in decreased pregnancies and in the retarded development of fetuses. These effects are thought to be due to an inhibition or delay in implantation which is also observed in rodents administered other antipsychotic drugs. In the rabbit, maternal toxicity, mortality, decreased weight gain, and embryotoxicity including increased resorptions were dose related. Because animal reproduction studies are not always predictive of human response, pimozide should be given to a pregnant woman only if the potential benefits of treatment clearly outweigh the potential risks.

**Labor and Delivery.** This drug has no recognized use in labor or delivery.

**Nursing Mothers.** It is not known whether pimozide is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity and unknown cardiovascular effects in the infant, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric Use** Although Tourette's Disorder most often has its onset between the ages of 2 and 15 years, information on the use and efficacy of ORAP in patients less than 12 years of age is limited.

Because its use and safety have not been evaluated in other childhood disorders, ORAP is not recommended for use in any condition other than Tourette's Disorder.

## ADVERSE REACTIONS

**General.** Extrapyramidal Reactions: Neuromuscular (extrapyramidal) reactions during the administration of ORAP (pimozide) have been reported frequently, often during the first few days of treatment. In most patients, these reactions involved Parkinson-like symptoms which, when first observed, were usually mild to moderately severe and usually reversible.

Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently. Severe extrapyramidal reactions have been reported to occur at relatively low doses. Generally the occurrence and severity of most extrapyramidal symptoms are dose related since they occur at relatively high doses and have been shown to disappear or become less severe when the dose is reduced. Administration of antiparkinson drugs such as benztropine mesylate or trihexyphenidyl hydrochloride may be required for control of such reactions. It should be noted that persistent extrapyramidal reactions have been reported and that the drug may have to be discontinued in such cases.

**Withdrawal Emergencies/Neurological Signs:** Generally, patients receiving short term therapy experience no problems with abrupt discontinuation of antipsychotic drugs. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain of these cases the dyskinetic movements are indistinguishable from the syndrome described below under "Tardive Dyskinesia" except for duration. It is not known whether gradual withdrawal of antipsychotic drugs will reduce the rate of occurrence of withdrawal emergent neurological signs but until further evidence becomes available, it seems reasonable to gradually withdraw use of ORAP.

**Tardive Dyskinesia:** ORAP may be associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmic involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk.

There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked.

It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the syndrome may not develop.

**Electrocardiographic Changes:** Electrocardiographic changes have been observed in clinical trials of ORAP in Tourette's Disorder and schizophrenia. These have included prolongation of the QT interval, flattening, notching and inversion of the T wave and the appearance of U waves. Sudden, unexpected deaths and grand mal seizure have occurred at doses above 20 mg/day.

**Neuroleptic Malignant Syndrome:** Neuroleptic malignant syndrome (NMS) has been reported with ORAP. (See WARNINGS for further information concerning NMS.)

**Hyperreflexia:** Hyperreflexia has been reported with other antipsychotic drugs.

**Clinical Trials:** The following adverse reaction tabulation was derived from 20 patients in a 6 week long placebo controlled clinical trial of ORAP in Tourette's Disorder.

Body System/ Adverse Reaction	Pimozide (N = 20)	Placebo (N = 20)
Body as a Whole		
Headache	1	2
Gastrointestinal		
Dry mouth	5	1
Diarrhea	1	0
Nausea	0	2
Vomiting	0	1
Constipation	4	2
Erections	0	1
Thirst	1	0
Appetite increase	1	0

Body/System/ Adverse Reaction	Pimozide (N = 20)	Placebo (N = 20)
Endocrine		
Menstrual disorder	0	1
Breast secretions	0	1
Musculoskeletal		
Muscle cramps	0	1
Muscle tightness	3	0
Sloped posture	2	0
CNS		
Drowsiness	7	3
Sadism	14	5
Insomnia	2	2
Dizziness	0	1
Anathisia	8	0
Rigidity	2	0
Speech disorder	2	0
Handwriting change	1	0
Akinesia	8	0
Psychiatric		
Depression	2	3
Excitement	0	1
Nervous	1	0
Adverse behavior	5	0
Other		
Special Sense		
Visual disturbance	4	0
Taste change	1	0
Sensitivity of eyes	1	0
to light		
Decreased accommodation	4	1
Spots before eyes	0	1
Urogenital		
Impotence	3	0

Because clinical investigational experience with ORAP in Tourette's Disorder is limited, uncommon adverse reactions may not have been detected. The physician should consider that other adverse reactions associated with antipsychotics may occur.

**Other Adverse Reactions** In addition to the adverse reactions listed above, those listed below have been reported in U.S. clinical trials of ORAP in conditions other than Tourette's Disorder.

**Body as a Whole:** Asthenia, chest pain, periorbital edema

**Cardiovascular/Respiratory:** Postural hypotension, hypotension, hypertension, tachycardia, palpitations

**Gastrointestinal:** Increased salivation, nausea, vomiting, anorexia, GI distress

**Endocrine:** Loss of libido

**Metabolic/Nutritional:** Weight gain, weight loss

**Central Nervous System:** Dizziness, tremor, parkinsonism, fainting, dyskinesia

**Psychiatric:** Excitement

**Skin:** Rash, sweating, skin irritation

**Special Senses:** Blurred vision, cataracts

**Urogenital:** Nocturia, urinary frequency

**Postmarketing Reports:** The following experiences were described in spontaneous postmarketing reports. These reports do not provide sufficient information to establish a clear causal relationship with the use of ORAP.

**Hematologic:** Hemolytic anemia

## OVERDOSAGE

In general, the signs and symptoms of overdosage with ORAP (pimozide) would be an exaggeration of known pharmacologic effects and adverse reactions, the most prominent of which would be: 1) electrocardiographic abnormalities, 2) severe extrapyramidal reactions, 3) hypotension, 4) a comatose state with respiratory depression.

In the event of overdosage, gastric lavage, establishment of a patent airway and, if necessary, mechanically-assisted respiration are advised. Electrocardiographic monitoring should commence immediately and continue until the ECG parameters are within the normal range. Hypotension and circulatory collapse may be counteracted by use of intravenous fluids, plasma, or concentrated albumin and vasopressor agents such as metaraminol, phenylephrine and norepinephrine. Epinephrine should not be used. In case of severe extrapyramidal reactions, antiparkinson medication should be administered. Because of the long half-life of pimozide, patients who take an overdose should be observed for at least 4 days. As with all drugs, the physician should consider contacting a poison control center for additional information on the treatment of overdose.

## DOSAGE AND ADMINISTRATION

Reliable dose response data for the effects of ORAP (pimozide) on tic manifestations in Tourette's Disorder patients below the age of twelve are not available. Consequently, the suppression of tics by ORAP requires a slow and gradual introduction of the drug. The patient's dose should be carefully adjusted to a point where the suppression of tics and the relief afforded is balanced against the untoward side effects of the drug.

An ECG should be done at baseline and periodically thereafter, especially during the period of dose adjustment (see WARNINGS and PRECAUTIONS—Laboratory Tests).

In general, treatment with ORAP should be initiated with a dose of 1 to 2 mg a day in divided doses. The dose may be increased thereafter every other day. Most patients are maintained at less than 0.2 mg/kg per day, or 10 mg/day, whichever is less. Doses greater than 0.2 mg/kg/day or 10 mg/day are not recommended.

Periodic attempts should be made to reduce the dosage of ORAP to see whether or not tics persist at the level and extent first identified. In attempts to reduce the dosage of ORAP, consideration should be given to the possibility that increases of tic intensity and frequency may represent a transient, withdrawal related phenomenon rather than a return of disease symptoms. Specifically, one to two weeks should be allowed to elapse before one concludes that an increase in tic manifestations is a function of the underlying disease syndrome rather than a response to drug withdrawal. A gradual withdrawal is recommended in any case.

## HOW SUPPLIED

ORAP (pimozide) 2 mg tablets, white, scored, imprint "LEMMON" and "ORAP-2"—NDC 57844-187-01, bottles of 100.

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1. Shapiro AK et al; *Pediatrics* 79:1032-1038, 1987.
2. Ross MS et al; *Am J Psychiatry* 135:585-587, 1978.

# Therapeutic Potential of Enhanced Dopaminergic Activity by Non-Precursors

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**CHAIRPERSON:** J. John Mann, M.D.

Sunday, May 13, 1990

Imperial Ballroom  
Sheraton Center  
New York, NY

1:00 - 4:00 p.m.

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**FACULTY:**

**J. John Mann, M.D.**

Professor of Psychiatry  
Director, Laboratories of Neuropharmacology  
Western Psychiatric Institute and Clinic  
University of Pittsburgh  
Pittsburgh, PA

**Ira Shoulson, M.D.**

Professor of Neurology, Pharmacology and Medicine  
University of Rochester School of Medicine  
Rochester, NY

**Professor Joseph Knoll**

Department of Pharmacology  
Semmelweis University of Medicine  
Budapest, Hungary

**Trey Sunderland, M.D.**

Chief, Uniton Geriatric Psychopharmacology  
Laboratory of Clinical Science  
National Institute of Mental Health

**Samuel Gershon, M.D.**

Vice President for Research  
University of Pittsburgh  
Pittsburgh, PA

**AGENDA:**

12:45 - 1:00 p.m.	Registration	
1:00 - 1:15 p.m.	Welcome and Introduction	J. John Mann, M.D.
1:15 - 1:45 p.m.	History of Basic Pharmacology of (-) - Deprenyl	Professor Joseph Knoll
1:45 - 2:15 p.m.	Effect of Deprenyl in Early Parkinson's Disease	Ira Shoulson, M.D.
2:15 - 2:30 p.m.	Refreshment Break	
2:30 - 3:00 p.m.	Efficacy and Side Effects of Deprenyl in Depression	J. John Mann, M.D.
3:00 - 3:30 p.m.	L-Deprenyl in Alzheimer's: an Innovative Therapy	Trey Sunderland, M.D.
3:30 - 3:50 p.m.	Potential New Applications for MAO-B Inhibitors	Samuel Gershon, M.D.
3:50 - 4:00 p.m.	Q&A/Discussion	J. John Mann, M.D.

- ♦ The American Psychiatric Association designates this continuing medical education activity for 3 credit hours in Category I of the Physician's Recognition Award of the American Medical Association and for the CME requirement of the APA.
- ♦ Refreshments will be served.
- ♦ Supported by an educational grant from Somerset Pharmaceuticals

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## Calendar

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*(Continued from page A24)*

August 23–26, World Psychiatric Association Regional Symposium—"Etiology of Mental Disorder," organized by the Department of Psychiatry, University of Oslo. Contact Prof. Einar Kringlen, WPA Regional Symposium Programme Committee, Department of Psychiatry, University of Oslo, P.O. Box 85, Vinderen, N-0319 Oslo 3, Norway; 47 2 146590.

### SEPTEMBER

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September 7–8, Long-Term Treatment of Affective Disorders: Review and Update, Ottawa. Contact Education Services, Royal Ottawa Hospital, 1145 Carling Avenue, Ottawa, Ontario, Canada, K1Z 7K4; 613-724-6525.

September 11–14, 6th International Conference on Phenothiazines and Structurally Related Psychotropic Compounds, Pasadena, California. Contact Dr. Hendrik Keyzer, Chemistry Department, California State University, 5151 State University Drive, Los Angeles, CA 90032; 213-343-2391.

September 16–19, annual meeting, American College of Emergency Physicians, San Francisco. Contact Colin C. Rorie, Jr., Ph.D., Executive Director, P.O. Box 619911, Dallas, TX 75261-9911; 214-550-0911.

September 20–21, 4th Leeds Psychopathology Symposium, "Delusions and Awareness of Reality," Leeds. Contact Mrs. Hilary L. Helme, Department of Continued Professional Education, The University, Leeds LS2 9JT, England; 0532 333233.

September 23–27, 2nd European Conference on Traumatic Stress, Noordwijkerhout, The Netherlands. Contact Jos M.P. Weerts, M.D., W. Barentszstr. 31-C, 3572 PB Utrecht, The Netherlands; 31-30-730811.

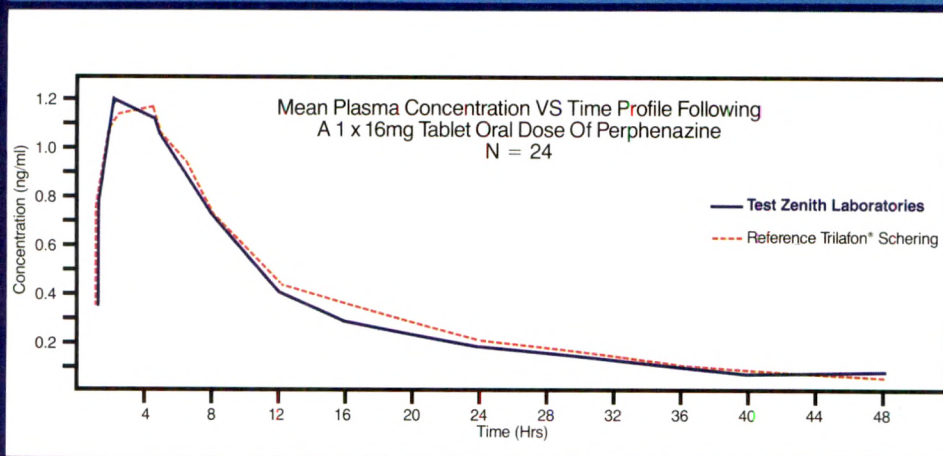
September 30–October 4, annual meeting, American Public Health Association, New York. Contact William H. McBeath, M.D., Executive Director, 1015 15th Street, N.W., Washington, DC 20005; 202-789-5600.





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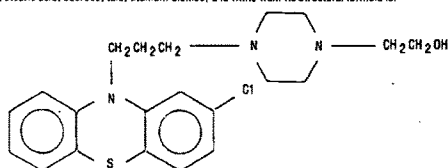
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## PERPHENAZINE TABLETS, USP

### DESCRIPTION

Perphenazine (4-[4-(2-chlorophenothiazin-10-yl)propyl]-1-piperazineethanol), is a piperazine phenothiazine having the chemical formula, C<sub>27</sub>H<sub>32</sub>N<sub>4</sub>ClS. It is available as oral tablets, containing 2 mg, 4 mg, 8 mg, and 16 mg of perphenazine. Inactive ingredients: acacia, carnauba wax, corn starch, FD&C Blue No. 2, FD&C Yellow No. 6, gelatin, lactose, magnesium stearate, microcrystalline cellulose, povidone, pregelatinized calcium carbonate, pregelatinized starch, sodium benzoate, sodium starch glycolate, stearic acid, sucrose, talc, titanium dioxide, and white wax. Its structural formula is:



### CLINICAL PHARMACOLOGY

Perphenazine has actions at all levels of the central nervous system, particularly the hypothalamus. However, the site and mechanism of action of therapeutic effect are not known.

#### INDICATIONS

Perphenazine is indicated for use in the management of the manifestations of psychotic disorders; and for the control of severe nausea and vomiting in adults. Perphenazine had not been shown effective in the management of behavioral complications in patients with mental retardation.

#### CONTRAINDICATIONS

Perphenazine products are contraindicated in comatose or greatly obtunded patients and in patients receiving large doses of central nervous system depressants (barbiturates, alcohol, narcotics, anxiolytics, or anticholinergics); in the presence of existing blood dyscrasias, bone marrow depression, or liver damage; and in patients who have shown hypersensitivity to perphenazine products, their components, or related compounds.

Perphenazine products are also contraindicated in patients with suspected or established subcortical brain damage, with or without hypothalamic damage, since a hyperthermic reaction with temperatures in excess of 104°F may occur in such patients, sometimes not until 14 to 16 hours after drug administration, since a hyperthermic reaction with temperatures in excess of 104°F may occur in such patients, sometimes not until 14 to 16 hours after drug administration. Total body ice-packing is recommended for such a reaction; antipyretics may also be used.

#### WARNINGS

Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment of established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome, and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these conditions, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to neuroleptic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to Information for Patients and ADVERSE REACTIONS.)

**Neuroleptic Malignant Syndrome (NMS):** A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS or hyperreflexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both severe medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens of uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

If hypotension develops, epinephrine should not be administered since its action is blocked and partially reversed by perphenazine. If a vasopressor is needed, norepinephrine may be used. Severe, acute hypotension has occurred with the use of perphenazines and is particularly likely to occur in patients with mitral insufficiency or pheochromocytoma. Rebound hypertension may occur in pheochromocytoma patients.

Perphenazine products can lower the convulsive threshold in susceptible individuals; they should be used with caution in alcohol withdrawal and in patients with convulsive disorders. If the patient is being treated with an anticonvulsant agent, increased dosage of that agent may be required when perphenazine products are used concomitantly.

Perphenazine products should be used with caution in patients with psychic depression.

Perphenazine may impair the mental and/or physical abilities required for the performance of hazardous tasks such as driving a car or operating machinery; therefore, the patient should be warned accordingly.

Perphenazine products are not recommended for children under 12 years of age.

**Usage in Pregnancy:** Safe use of perphenazine during pregnancy and lactation has not been established, therefore, in administering the drug to pregnant patients, nursing mothers, or women who may become pregnant, the possible benefits must be weighed against the possible hazards to mother and child.

#### PRECAUTIONS

The possibility of suicide in depressed patients remains during treatment and until significant remission occurs. This type of patient should not have access to large quantities of this drug.

As with all phenothiazine compounds, perphenazine should not be used indiscriminately. Caution should be observed in giving it to patients who have previously exhibited severe adverse reactions to other phenothiazines. Some of the untoward actions of perphenazine tend to appear more frequently when high doses are used. However, as with other phenothiazine compounds, patients receiving perphenazine products in any dosage should be kept under close supervision. Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers and prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomasia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

The antiemetic effect of perphenazine may obscure signs of toxicity due to overdosage of other drugs, or render more difficult the diagnosis of disorders such as brain tumors or intestinal obstruction.

A significant, not otherwise explained, rise in body temperature may suggest individual intolerance to perphenazine, in which case it should be discontinued. Patients on large doses of a phenothiazine drug who are undergoing surgery should be watched carefully for possible hypotensive phenomena. Moreover, reduced amounts of anesthetics or central nervous system depressants may be necessary.

Since phenothiazines and central nervous system depressants (opiates, anxiolytics, barbiturates) can potentiate each other, less than the usual dosage of the added drug is recommended, and caution is advised, when they are administered concomitantly.

Use with caution in patients who are receiving atropine or related drugs because of additive anticholinergic effects and also in patients who will be exposed to extreme heat or phosphorus insecticides.

The use of alcohol should be avoided, since additive effects and hypotension may occur. Patients should be cautioned that their response to alcohol may be increased while they are being treated with perphenazine products. The risk of suicide and the danger of overdosage may be increased in patients who use alcohol excessively due to its potentiation of the drug's effect.

Blood counts and hepatic and renal functions should be checked periodically. The appearance of signs of blood dyscrasias requires the discontinuance of the drug and institution of appropriate therapy. If abnormalities in hepatic tests occur, perphenazine treatment should be discontinued. Renal function in patients on long-term therapy should be monitored; if blood urea nitrogen (BUN) becomes abnormal, treatment with the drug should be discontinued.

The use of phenothiazine derivatives in patients with diminished renal function should be undertaken with caution.

Use with caution in patients suffering from respiratory impairment due to acute pulmonary infections, or in chronic respiratory disorders such as severe asthma or emphysema.

In general, phenothiazines, including perphenazine, do not produce psychic depression. Gastritis, nausea and vomiting, dizziness, and tremulousness have been reported following abrupt cessation of high-dose therapy. Reports suggest that these symptoms can be reduced by continuing concomitant antiparkinsonian agents for several weeks after the phenothiazine is withdrawn. The possibility of liver damage, corneal and lenticular deposits, and irreversible dyskinesias should be kept in mind when patients are on long-term therapy. Because photosensitivity has been reported, undue exposure to the sun should be avoided during phenothiazine treatment.

**Information for Patients:** This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Given the likelihood that a substantial proportion of patients exposed chronically to neuroleptics will develop tardive dyskinesia, it is advised that all patients on chronic use of this drug be warned, if possible, of the risk. The decision to inform patients and/or their guardians must obviously take into account the clinical circumstances and the competency of the patient to understand the information provided.

#### ADVERSE REACTIONS

Not all of the following adverse reactions have been reported with this specific drug; however, pharmacological similarities among various phenothiazine derivatives require that each be considered. In the case of the piperazine group (of which perphenazine is an example), the extrapyramidal symptoms are more common, and others (e.g., sedative effects, jaundice, and blood dyscrasias) are less frequently seen.

**CNS Effects:** Extrapyramidal reactions: opisthotonus, trismus, torticollis, retrocollis, aching and numbness of the limbs, motor restlessness, oculogyric crisis, hyperreflexia, dystonia, oculoclonus, discoloration, aching and rounding of the tongue, tonic spasm of the masticatory muscles, tight feeling in the throat, slurred speech, dysphagia, akathisia, dyskinesia, parkinsonism, and akata. Their incidence and severity usually increase with an increase in dosage, but there is considerable individual variation in the tendency to develop such symptoms. Extrapyramidal symptoms can usually be controlled by the concomitant use of effective antipsychotic drugs, such as benztropine mesylate, and/or by reduction in dosage. In some instances, however, these extrapyramidal reactions may persist after discontinuation of treatment with perphenazine.

**Persistent Tardive Dyskinesia:** As with all antipsychotic agents, tardive dyskinesia may appear in some patients on long-term therapy or may appear after drug therapy has been discontinued. Although the risk appears to be greater in elderly patients on high-dose therapy, especially females, it may occur in either sex and in children. The symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterized by rhythmic, involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of the extremities. There is no known effective treatment for tardive dyskinesia, antiparkinsonian agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, it is suggested that the dosage of the agent, or switch to a different antipsychotic agent, the syndrome may be masked. It has been reported that fine, vermicular movements of the tongue may be an early sign of the syndrome, and if the medication is stopped at that time the syndrome may not develop. Other CNS effects include cerebral edema, abnormality of cerebrospinal fluid proteins; convulsive seizures, particularly in patients with EEG abnormalities or a history of such disorders; and headaches.

**Neuroleptic malignant syndrome** has been reported in patients treated with neuroleptic drugs. (See **WARNINGS**). Drowsiness may occur, particularly during the first or second week, after which it generally disappears. If troublesome, lower the dosage. Hypnotic effects appear to be minimal, especially in patients who are permitted to remain active.

Adverse behavioral effects include paradoxical exacerbation of psychotic symptoms, catatonic-like states, paranoid reactions, lethargy, paradoxical excitement, restlessness, hyperactivity, nocturnal confusion, bizarre dreams, and insomnia. Hyperreflexia has been reported in the newborn when a phenothiazine was used during pregnancy.

**Autonomic Effects:** dry mouth or salivation, nausea, vomiting, diarrhea, anorexia, constipation, obstipation, fecal impaction, urinary retention, frequency or incontinence, bladder paralysis, polyuria, nasal congestion, pallor, myosis, mydriasis, blurred vision, glaucoma, perspiration, hypertension, hypotension and change in pulse rate occasionally may occur. Significant autonomic effects have been infrequent in patients receiving less than 24 mg of perphenazine daily. Adynamic ileus occasionally occurs with phenothiazine therapy and if severe can result in complicated ileus and death. It is of particular concern in psychiatric patients, who may fail to seek treatment of the condition.

**Allergic Effects:** urticaria, erythema, eczema, exfoliative dermatitis, pruritus, photosensitivity, asthma, fever, angioedema, laryngospasm, edema, and anaphylactic shock, contact dermatitis in nursing personnel administering the drug, and in extremely rare instances, individual idiosyncrasy or hypersensitivity to phenothiazines has resulted in cerebral edema, circulatory collapse, and death.

**Endocrine Effects:** lactation, galactorrhea, moderate breast enlargement in females and gynecomasia in males on large doses, disturbances in the menstrual cycle, amenorrhea, changes in libido, inhibition of ejaculation, syndrome of inappropriate ADH (antidiuretic hormone) secretion, false positive pregnancy tests, hyperglycemia, hypoglycemia, glycosuria.

**Cardiovascular Effects:** postural hypotension, tachycardia (especially with sudden marked increase in dosage), bradycardia, cardiac arrest, faintness, and dizziness. Occasionally the hypotensive effect may produce a shock-like condition. ECG changes, nonspecific (quinidine-like effect) usually reversible, have been observed in some patients receiving phenothiazine tranquilizers. Sudden death has occasionally been reported in patients who have received phenothiazines. In some cases the death was apparently due to cardiac arrest, in others, the cause appeared to be asphyxia due to failure of the cough reflex. In some patients, the cause could not be determined nor could it be established that the death was due to the phenothiazine.

**Hematological Effects:** agranulocytosis, eosinophilia, leukopenia, hemolytic anemia, thrombocytopenic purpura, and pancytopenia. Myelosuppression and agranulocytosis have occurred between the fourth and tenth weeks of therapy. Patients should be watched closely especially during that period for the sudden appearance of sore throat or signs of infection. If white blood cells and differential cell counts show significant cellular depression, discontinue the drug and start appropriate therapy. However, a slightly lowered white count is not in itself an indication to discontinue the drug.

**Other Effects:** Special considerations in long-term therapy include pigmentation of the skin, occurring chiefly in the exposed areas, ocular changes consisting of deposition of fine particulate matter in the cornea and lens, progressing in more severe cases to star-shaped lenticular opacities, epithelial keratopathies, and pigmentary retinopathy. Also noted: peripheral edema, reversed erythema nigricans effect, increase in PBI not attributable to an increase in thyroxine, parotid swelling (rare), hyperreflexia, systemic lupus erythematosus-like syndrome, increases in appetite and weight, polyphagia, photophobia, and muscle weakness. Liver damage (biliary stasis) may occur. Jaundice may occur, usually between the second and fourth weeks of treatment and is regarded as a hypersensitivity reaction. Incidence is low. The clinical picture resembles infectious hepatitis but with laboratory features of obstructive jaundice. It is usually reversible, however, chronic jaundice has been reported.

#### OVERDOSAGE

In the event of overdosage, emergency treatment should be started immediately. All patients suspected of having taken an overdose should be hospitalized as soon as possible.

**Manifestations:** Overdosage of perphenazine primarily involves the extrapyramidal mechanism and produces the same side effects described under **ADVERSE REACTIONS**, but to a more marked degree. It is usually evidenced by stupor or coma; children may have convulsive seizures.

**Treatment:** Treatment is symptomatic and supportive. There is no specific antidote. The patient should be induced to vomit even if emesis has occurred spontaneously. Pharmacologic vomiting by the administration of ipecac syrup is a preferred method. It should be noted that ipecac has a central mode of action in addition to its local gastric irritant properties, and the central mode of action may be blocked by the antiemetic effect of perphenazine products. Vomiting should not be induced in patients with impaired consciousness. The action of ipecac is facilitated by physical activity and by the administration of 8 to 12 fluid ounces of water. If emesis does not occur within 15 minutes, the dose of ipecac should be repeated. Precautions against aspiration must be taken, especially in infants and children. Following emesis, any drug remaining in the stomach may be absorbed by activated charcoal administered as a slurry with water. If vomiting is unsuccessful or contraindicated, gastric lavage should be performed. Isotonic and one-half isotonic saline are the lavage solutions of choice. Saline cathartics, such as milk of magnesia, draw water into the bowel by osmosis and therefore may be valuable for their action in rapid dilation of bowel content. Standard measures (syringe, enemas, fluids, corticosteroids) should be used to manage circulatory shock or metabolic acidosis. An open airway and adequate fluid intake should be maintained. Body temperature should be regulated. Hypothermia is expected, but severe hyperthermia may occur and must be treated vigorously. (See **CONTRAINDICATIONS**.)

An electrocardiogram should be taken and close monitoring of cardiac function instituted if there is any sign of abnormality. Cardiac arrhythmias may be treated with neostigmine, pyridostigmine, or propranolol. Digitalis should be considered for cardiac failure. Close monitoring of cardiac function is advisable for not less than five days. Vasopressors such as norepinephrine may be used to treat hypotension, but epinephrine should NOT be used.

Anticonvulsants (an inhalation anesthetic, diazepam, or paraldehyde) are recommended for control of convulsions, since perphenazine increases the central nervous system depressant action, but not the anticonvulsant action of barbiturates. If acute parkinson-like symptoms result from perphenazine intoxication, benztropine mesylate or diphenhydramine may be administered.

Central nervous system depression may be treated with non-convulsant doses of CNS stimulants. Avoid stimulants that may cause convulsions (e.g., picrotoxin and pentyltetrazolol).

Signs of arousal may not occur for 48 hours.

Dialysis is of no value because of low plasma concentrations of the drug.

Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase. Deaths by deliberate or accidental overdosage have occurred with this class of drug.

#### DOSEAGE AND ADMINISTRATION

Dosage must be individualized and adjusted according to the severity of the condition and the response obtained. As with all potent drugs, the best dose is the lowest dose that will produce the desired clinical effect. Since extrapyramidal symptoms increase in frequency and severity with increased dosage, it is important to employ the lowest effective dose. These symptoms have disappeared upon reduction of dosage, withdrawal of the drug or administration of an anti-parkinsonian agent.

Prolonged administration of doses exceeding 24 mg daily should be reserved for hospitalized patients or patients under continued observation for early detection and management of adverse reactions. An antiparkinsonian agent, such as trihexyphenidyl hydrochloride or benztropine mesylate, is valuable in controlling drug-induced extrapyramidal symptoms.

Suggested dosages for various conditions follow:

**Moderately disturbed non-hospitalized psychotic patients:** 4 to 8 mg b.i.d. initially; reduce as soon as possible to minimum effective dosage.

**Hospitalized psychotic patients:** 8 to 16 mg b.i.d. to q.i.d.; avoid dosages in excess of 64 mg daily.

**Severe nausea and vomiting in adults:** 8 to 16 mg daily in divided doses; 24 mg occasionally may be necessary; early dosage reduction is desirable.

#### HOW SUPPLIED

Available as a round, gray tablet imprinted 3667/2 on one side and Zenith logo on opposite side containing 2 mg of perphenazine, USP, as a round gray tablet imprinted 3668/4 on one side and Zenith logo on opposite side containing 4 mg of perphenazine, USP, as a round, gray tablet imprinted 3669/8 on one side and Zenith logo on opposite side containing 8 mg of perphenazine, USP, as a round, gray tablet imprinted 3670/16 on one side and Zenith logo on opposite side containing 16 mg of perphenazine, USP. All strengths are packaged in bottles of 100 and 500 tablets.

#### NDC Numbers:

2 mg	4 mg
0172-3667-50 (100's)	0172-3668-50 (100's)
0172-3667-70 (500's)	0172-3668-70 (500's)
8 mg	16 mg
0172-3669-50 (100's)	0172-3670-50 (100's)
0172-3669-70 (500's)	0172-3670-70 (500's)

**PHARMACIST:** Dispense in light, light-resistant container as defined in the USP. Use child resistant closure.

**CAUTION:** Federal law prohibits dispensing without prescription.

#### FINAL DOSE FORM

#### MANUFACTURED BY

ZENITH LABORATORIES, INC.

NORTHVALE, NEW JERSEY 07647

PERPHENAZINE TABLETS USP

0172

Revised 9/88

02



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**LOW AVAILABLE FOR DEPRESSION IN A WIDE RANGE OF PATIENTS**

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Feeling better  
Living better

**NEW Wellbutrin<sup>®</sup>**

(BUPROPION HCl)

**helps clear  
depression with  
few life-style  
disruptions.**

See brief summary of full prescribing information  
on last pages of this advertisement.

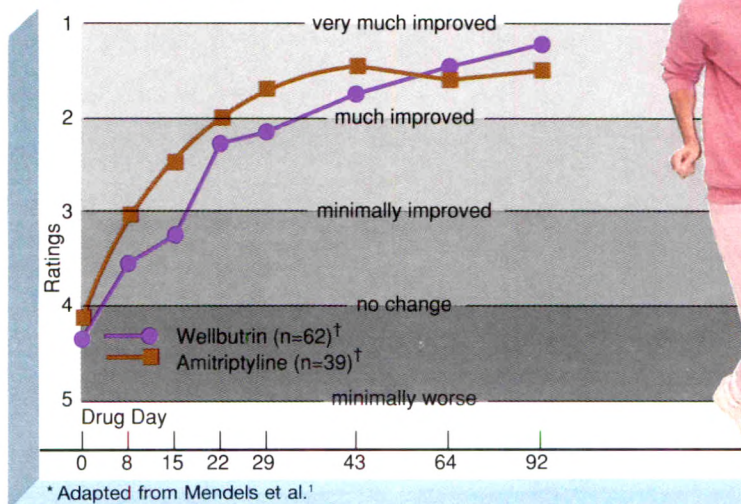


Chemically unique WELLBUTRIN

# Helps clear depression with few life-style disruptions.

**Relieves depression as  
effectively as amitriptyline.**

Clinical Global Improvement\*

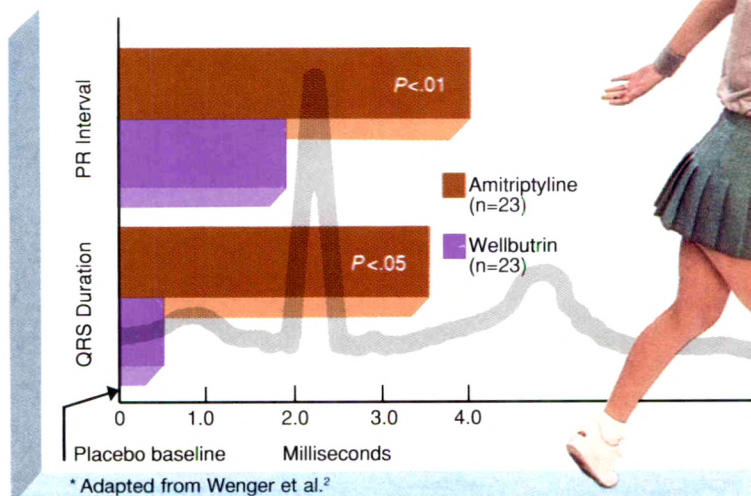


<sup>†</sup>Dosages were 300 to 450 mg/day for WELLBUTRIN, 75 to 150 mg/day for amitriptyline.

Please review IMPORTANT CONSIDERATIONS BEFORE  
PRESCRIBING WELLBUTRIN and brief summary on the last  
pages of this advertisement before prescribing WELLBUTRIN.

**Relieves depression with  
no clinically significant effect  
on cardiac conduction.**

Average Change in EKG Parameters  
from Baseline Values During Treatment\*

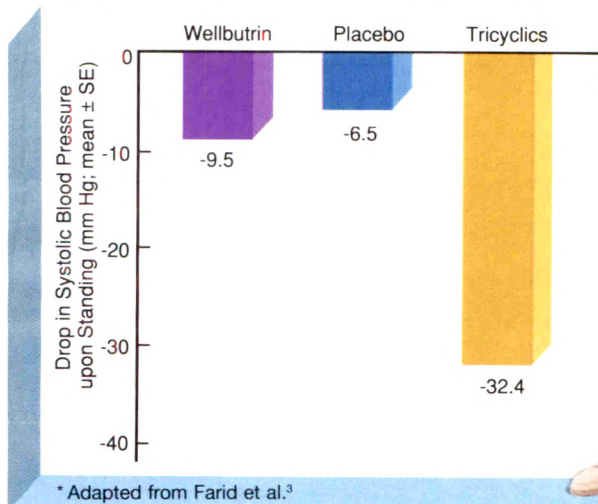


*"By contrast, the present results with bupropion support the in vitro data demonstrating that this antidepressant lacks these undesirable electrophysiologic properties, and imply that bupropion has a substantially wider margin of safety in man than amitriptyline with regard to cardiac conduction."*<sup>2</sup>

# Feeling better Living better

**Relieves depression with  
no clinically significant  
orthostatic hypotension.**

Orthostatic Blood Pressure Change (mm Hg)\*



**NEW** **Wellbutrin<sup>®</sup>**  
(BUPROPION HCl)

**Helps clear depression with few life-style disruptions.**

See brief summary of full prescribing information  
on last pages of this advertisement.

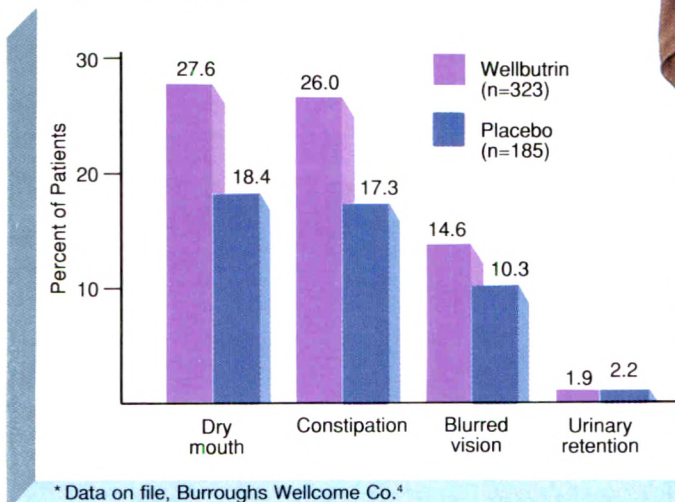


Chemically unique WELLBUTRIN

# Helps clear depression with few life-style disruptions.

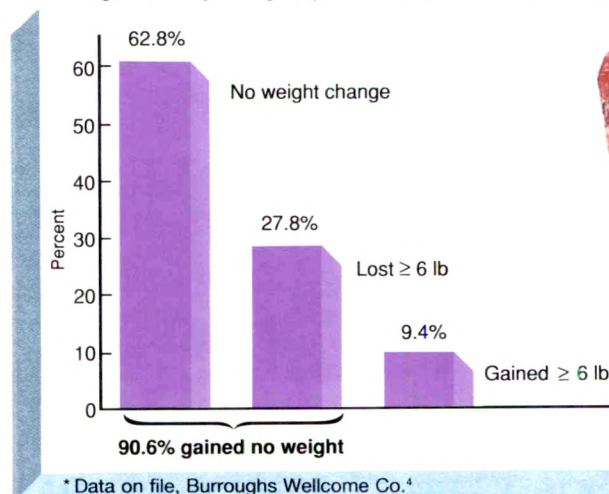
## Relieves depression with few anticholinergic side effects.

Percent Difference in Anticholinergic Effects  
Relative to Placebo\*



## Relieves depression with little or no weight gain.

Change in Body Weight (percent of patients; n=341)\*

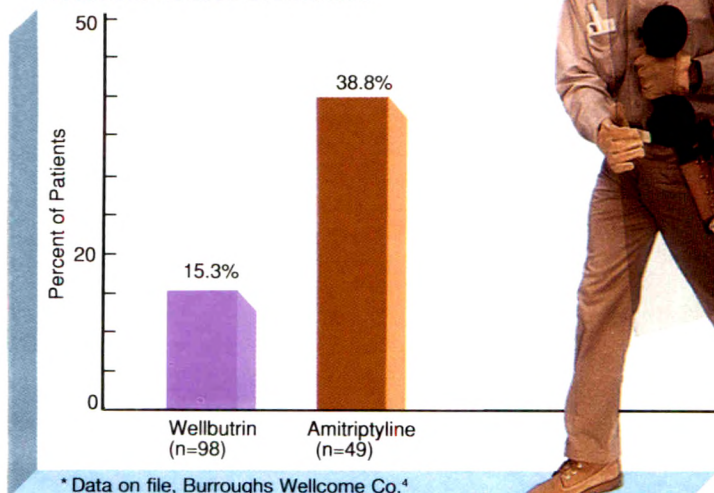




# Feeling better Living better

**Relieves depression with little  
or no daytime drowsiness.**

Percent of Patients Reporting  
Treatment-Related Drowsiness\*



In placebo-controlled clinical trials, the incidence of drowsiness\* for patients treated with WELLBUTRIN was 19.8%, versus 19.5% for those receiving placebo.

**Agitation and Insomnia:** A substantial proportion of patients treated with WELLBUTRIN experience some degree of increased restlessness, agitation, anxiety, and insomnia, especially shortly after initiation of treatment. In clinical studies, these symptoms were sometimes of sufficient magnitude to require treatment with sedative/hypnotic drugs. In approximately 2% of patients, symptoms were sufficiently severe to require discontinuation of WELLBUTRIN treatment.

\*As with all drugs in this category, patients should be cautioned that the ability to perform tasks requiring judgment or motor and cognitive skills may be impaired.

**NEW**

# Wellbutrin<sup>®</sup>

(BUPROPION HCl)

**Helps clear depression with few life-style disruptions.**

See brief summary of full prescribing information  
on last pages of this advertisement.



Feeling better  
Living better

## Wellbutrin helps clear depression with few life-style disruptions.

### Important considerations before prescribing WELLBUTRIN.

#### Patient Selection Criteria

WELLBUTRIN is contraindicated in patients

- with a seizure disorder
- with a current or prior diagnosis of bulimia or anorexia nervosa
- on monoamine oxidase (MAO) inhibitor therapy
- who are allergic to it

(See CONTRAINDICATIONS section of full prescribing information.)

WELLBUTRIN should be administered with extreme caution to patients

- with a history of seizure, cranial trauma, or other factors that predispose toward seizure
- taking other agents or other treatment regimens that may lower seizure threshold

(See WARNINGS section of full prescribing information.)

#### Overdosage

In 13 cases of overdose involving WELLBUTRIN, there were no deaths or lasting sequelae.

#### Seizures

A wide range of seizure rates has been reported with antidepressant therapy with some reports as low as 0.1%. The incidence of seizures with WELLBUTRIN is approximately 0.4%, which may be as much as fourfold higher than some other antidepressants, although no direct comparative studies have been conducted.

#### Dosage and Administration

The recommended starting dose of WELLBUTRIN is 200 mg/day given as 100 mg b.i.d. Based on clinical response, this dose may be increased to 300 mg/day given as 100 mg t.i.d. no sooner than three days after beginning therapy.

#### Dosing Regimen

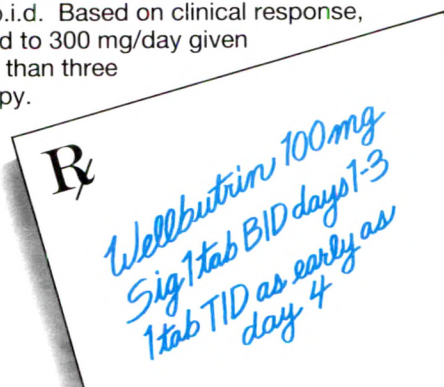
Treatment Day	Total Daily Dose	Tablet Strength	Number of Tablets		
			Morning	Midday	Evening
1-3	200 mg	100 mg	1	0	1
4	300 mg	100 mg	1	1	1

An increase in dosage, up to a maximum of 450 mg/day, given in divided doses of not more than 150 mg each, may be considered for patients in whom no clinical improvement is noted after several weeks of treatment at 300 mg/day. Increases in dose should not exceed 100 mg/day in a three-day period. WELLBUTRIN is available in both 75 mg and 100 mg tablets.

**Important: No single dose of WELLBUTRIN should exceed 150 mg, because a higher incidence of seizures has been observed in patients receiving higher individual doses of WELLBUTRIN. For this reason, too, patients should be reminded that they should not double up on any dose because they missed a previous one. Dosage should not exceed 450 mg per day (see WARNINGS).**

Clinical trials involving more than 7,000 depressed patients and over 200 investigators demonstrated that **WELLBUTRIN relieves depression in a wide range of patients:**

- with no clinically significant effects on cardiac conduction
- with no clinically significant orthostatic hypotension
- with few anticholinergic side effects
- with little or no weight gain
- with little or no daytime drowsiness



**NEW**  
**Wellbutrin**<sup>®</sup>  
(BUPROPION HCl)

See brief summary of full prescribing information on last pages of this advertisement.

## WELLBUTRIN® (BUPROPION HYDROCHLORIDE) Tablets

Before prescribing, please consult complete product information, a summary of which follows:

**INDICATIONS AND USAGE:** Wellbutrin is indicated for the treatment of depression. A physician considering the initiation of Wellbutrin should be aware that the drug may cause generalized seizures with an approximate incidence of 0.4% (4/1000). This incidence may exceed that of other antidepressants as much as fourfold. This relative risk is only an approximation since no direct comparative studies have been conducted.

**CONTRAINDICATIONS:** Wellbutrin is contraindicated in patients: with a seizure disorder; with a current or prior diagnosis of bulimia or anorexia nervosa, because of a higher incidence of seizures noted in such patients; who have shown an allergic response to it; or who are currently being treated with an MAO inhibitor. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with Wellbutrin.

### WARNINGS:

**SEIZURES:** Wellbutrin is associated with seizures in approximately 0.4% (4/1000) of patients treated at doses up to 450 mg/day. This incidence of seizures may exceed that of other marketed antidepressants by as much as fourfold. This relative risk is only an approximate estimate because no direct comparative studies have been conducted. The estimated seizure incidence for Wellbutrin increases almost tenfold between 450 and 600 mg/day, which is twice the usually required daily dose (300 mg) and one and one-third the maximum recommended daily dose (450 mg). Given the wide variability among individuals and their capacity to metabolize and eliminate drugs, this disproportionate increase in seizure incidence with dose increment calls for caution in dosing.

During the pre-approval evaluation period, 25 among approximately 2400 patients treated with Wellbutrin experienced seizures. At the time of seizure, 7 patients were receiving daily doses of 450 mg or below, for an incidence of 0.33% (3/1000) within the recommended dose range. Twelve (12) patients experienced seizures at 600 mg per day (2.3% incidence); 6 additional patients had seizures at daily doses between 600 and 900 mg (2.8% incidence).

A separate, prospective study was conducted to determine the incidence of seizure during an 8 week treatment exposure in approximately 3200 additional patients who received daily doses of up to 450 mg. Patients were permitted to continue treatment beyond 8 weeks if clinically indicated. Eight (8) seizures occurred during the initial 8 week treatment period and 5 seizures were reported in patients continuing treatment beyond 8 weeks, resulting in a total seizure incidence of 0.4%.

The risk of seizure appears to be strongly associated with dose and the presence of predisposing factors. A significant predisposing factor (e.g., history of head trauma or prior seizure, CNS tumor, concomitant medications that lower seizure threshold, etc.) was present in approximately one-half of the patients experiencing a seizure. Sudden and large increments in dose may contribute to increased risk. While many seizures occurred early in the course of treatment, some seizures did occur after several weeks at fixed dose.

**Recommendations for reducing the risk of seizure:** Retrospective analysis of clinical experience gained during the development of Wellbutrin suggests that the risk of seizure may be minimized if (1) the total daily dose of Wellbutrin does not exceed 450 mg, (2) the daily dose is administered t.i.d., with each single dose not to exceed 150 mg to avoid high peak concentrations of bupropion and/or its metabolites, and (3) the rate of incrementation of dose is very gradual. Extreme caution should be used when Wellbutrin is (1) administered to patients with a history of seizure, cranial trauma, or other predisposition(s) toward seizure, or (2) prescribed with other agents (e.g., antipsychotics, other antidepressants, etc.) or treatment regimens (e.g., abrupt discontinuation of a benzodiazepine) that lower seizure threshold.

**Potential for Hepatotoxicity:** In rats receiving large doses of bupropion chronically, there was an increase in incidence of hepatic hyperplastic nodules and hepatocellular hypertrophy. In dogs receiving large doses of bupropion chronically, various histologic changes were seen in the liver, and laboratory tests suggesting mild hepatocellular injury were noted. Although scattered abnormalities in liver function tests were detected in patients participating in clinical trials, there is no clinical evidence that bupropion acts as a hepatotoxin in humans.

### PRECAUTIONS:

#### General:

**Agitation and Insomnia:** A substantial proportion of patients treated with Wellbutrin experience some degree of increased restlessness, agitation, anxiety, and insomnia, especially shortly after initiation of treatment. In clinical studies, these symptoms were sometimes of sufficient magnitude to require treatment with sedative/hypnotic drugs. In approximately 2% of patients, symptoms were sufficiently severe to require discontinuation of Wellbutrin treatment.

**Psychosis, Confusion, and Other Neuropsychiatric Phenomena:** Patients treated with Wellbutrin have been reported to show a variety of neuropsychiatric signs and symptoms including delusions, hallucinations, psychotic episodes, confusion, and paranoia. Because of the uncontrolled nature of many studies, it is impossible to provide a precise estimate of the extent of risk imposed by treatment with Wellbutrin. In several cases, neuropsychiatric phenomena abated upon dose reduction and/or withdrawal of treatment.

**Activation of Psychosis and/or Mania:** Antidepressants can precipitate manic episodes in Bipolar Manic Depressive patients during the depressed phase of their illness and may activate latent psychosis in other susceptible patients. Wellbutrin is expected to pose similar risks.

**Altered Appetite and Weight:** A weight loss of greater than 5 pounds occurred in 28% of Wellbutrin patients. This incidence is approximately double that seen in comparable patients treated with tricyclics or placebo. Furthermore, while 34.5% of patients receiving tricyclic antidepressants gained weight, only 9.4% of patients treated with Wellbutrin did. Consequently, if weight loss is a major presenting sign of a patient's depressive illness, the anorectic and/or weight reducing potential of Wellbutrin should be considered.

**Suicide:** The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Accordingly, prescriptions for Wellbutrin should be written for the smallest number of tablets consistent with good patient management.

**Use in Patients with Systemic Illness:** There is no clinical experience establishing the safety of Wellbutrin in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, care should be exercised if it is used in these groups. Wellbutrin was well tolerated in patients who had previously developed orthostatic hypotension while receiving tricyclic antidepressants.

Because bupropion HCl and its metabolites are almost completely excreted through the kidney and metabolites are likely to undergo conjugation in the liver prior to urinary excretion, treatment of patients with renal or hepatic impairment should be initiated at reduced dosage as bupropion and its metabolites may accumulate in such patients beyond concentrations expected in patients without renal or hepatic impairment. The patient should be closely monitored for possible toxic effects of elevated blood and tissue levels of drug and metabolites.

### Information for Patients:

Patients should be instructed to take Wellbutrin in equally divided doses three or four times a day to minimize the risk of seizure.

Patients should be told that any CNS-active drug like Wellbutrin may impair their ability to perform tasks requiring judgment or motor and cognitive skills. Consequently, until they are reasonably certain that Wellbutrin does not adversely affect their performance they should refrain from driving an automobile or operating complex, hazardous machinery.

Patients should be told that the use and cessation of use of alcohol may alter the seizure threshold, and, therefore, that the consumption of alcohol should be minimized, and, if possible, avoided completely.

Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

**Drug Interactions:** No systematic data have been collected on the consequences of the concomitant administration of Wellbutrin and other drugs.

However, animal data suggest that Wellbutrin may be an inducer of drug metabolizing enzymes. This may be of potential clinical importance because the blood levels of co-administered drugs may be altered.

Alternatively, because bupropion is extensively metabolized, the co-administration of other drugs may affect its clinical activity. In particular, care should be exercised when administering drugs known to affect hepatic drug metabolizing enzyme systems (e.g., carbamazepine, cimetidine, phenobarbital, phenytoin).

Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAO inhibitor phenelzine (see CONTRAINDICATIONS).

Limited clinical data suggest a higher incidence of adverse experiences in patients receiving concurrent administration of Wellbutrin and L-dopa. Administration of Wellbutrin to patients receiving L-dopa concurrently should be undertaken with caution, using small initial doses and small gradual dose increases.

Concurrent administration of Wellbutrin and agents which lower seizure threshold should be undertaken only with extreme caution (see WARNINGS). Low initial dosing and small gradual dose increases should be employed.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Lifetime carcinogenicity studies were performed in rats and mice at doses up to 300 and 150 mg/kg/day, respectively. In the rat study there was an increase in nodular proliferative lesions of the liver at doses of 100 to 300 mg/kg/day; lower doses were not tested. The question of whether or not such lesions may be precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in either study.

Bupropion produced a borderline positive response (2-3 times control mutation rate) in some strains in the Ames bacterial mutagenicity test, and a high oral dose (300, but not 100 or 200 mg/kg) produced a low incidence of chromosomal aberrations in rats. The relevance of these results in estimating the risk of human exposure to therapeutic doses is unknown.

A fertility study was performed in rats; no evidence of impairment of fertility was encountered at oral doses up to 300 mg/kg/day.

**Pregnancy: Teratogenic Effects:** Pregnancy Category B: Reproduction studies have been performed in rabbits and rats at doses up to 15-45 times the human daily dose and have revealed no definitive evidence of impaired fertility or harm to the fetus due to bupropion. (In rabbits, a slightly increased incidence of fetal abnormalities was seen in two studies, but there was no increase in any specific abnormality). There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

**Labor and Delivery:** The effect of Wellbutrin on labor and delivery in humans is unknown.

**Nursing Mothers:** Because of the potential for serious adverse reactions in nursing infants from Wellbutrin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric Use:** The safety and effectiveness of Wellbutrin in individuals under 18 years old have not been established.

**Use in the Elderly:** Wellbutrin has not been systematically evaluated in older patients.

**ADVERSE REACTIONS:** (See also WARNINGS and PRECAUTIONS) Adverse events commonly encountered in patients treated with Wellbutrin are agitation, dry mouth, insomnia, headache/migraine, nausea/vomiting, constipation, and tremor.

Adverse events were sufficiently troublesome to cause discontinuation of Wellbutrin treatment in approximately ten percent of the 2400 patients and volunteers who participated in the product's pre-approval clinical trials. The more common events causing discontinuation include neuropsychiatric disturbances (3.0%), primarily agitation and abnormalities in mental status; gastrointestinal disturbances (2.1%), primarily nausea and vomiting; neurological disturbances (1.7%), primarily seizures, headaches, and sleep disturbances; and dermatologic problems (1.4%), primarily rashes. It is important to note, however, that many of these events occurred at doses that exceed the recommended daily dose.



The table below is presented solely to indicate the relative frequency of adverse events reported in representative controlled clinical studies conducted to evaluate the safety and efficacy of Wellbutrin under relatively similar conditions of daily dosage (300-600 mg), setting, and duration (3-4 weeks). The figures cited cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors must differ from those which prevailed in the clinical trials. These incidence figures also cannot be compared with those obtained from other clinical studies involving related drug products as each group of drug trials is conducted under a different set of conditions.

Finally, it is important to emphasize that the tabulation does not reflect the relative severity and/or clinical importance of the events. A better perspective on the serious adverse events associated with the use of Wellbutrin is provided in the WARNINGS and PRECAUTIONS sections.

**TREATMENT EMERGENT ADVERSE EXPERIENCE INCIDENCE  
IN PLACEBO-CONTROLLED CLINICAL TRIALS\***  
(Percent of Patients Reporting)

Adverse Experience	Wellbutrin Patients (n = 323)	Placebo Patients (n = 185)	Adverse Experience	Wellbutrin Patients (n = 323)	Placebo Patients (n = 185)
<b>CARDIOVASCULAR</b>			<b>Dry Mouth</b>	27.6	18.4
Cardiac Arrhythmias	5.3	4.3	Excessive Sweating	22.3	14.6
Dizziness	22.3	16.2	Headache/Migraine	25.7	22.2
Hypertension	4.3	1.6	Impaired Sleep Quality	4.0	1.6
Hypotension	2.5	2.2	Increased Salivary Flow	3.4	3.8
Palpitations	3.7	2.2	Insomnia	18.6	15.7
Syncope	1.2	0.5	Muscle Spasms	1.9	3.2
Tachycardia	10.8	8.6	Pseudoparkinsonism	1.5	1.6
<b>DERMATOLOGIC</b>			Sedation	19.8	19.5
Pruritus	2.2	0.0	Sensory Disturbance	4.0	3.2
Rash	8.0	6.5	Tremor	21.1	7.6
<b>GASTROINTESTINAL</b>			<b>NEUROPSYCHIATRIC</b>		
Anorexia	18.3	18.4	Agitation	31.9	22.2
Appetite Increase	3.7	2.2	Anxiety	3.1	1.1
Constipation	26.0	17.3	Confusion	8.4	4.9
Diarrhea	6.8	8.6	Decreased Libido	3.1	1.6
Dyspepsia	3.1	2.2	Delusions	1.2	1.1
Nausea/Vomiting	22.9	18.9	Disturbed Concentration	3.1	3.8
Weight Gain	13.6	22.7	Euphoria	1.2	0.5
Weight Loss	23.2	23.2	Hostility	5.6	3.8
<b>GENITOURINARY</b>			<b>NONSPECIFIC</b>		
Impotence	3.4	3.1	Fatigue	5.0	8.6
Menstrual Complaints	4.7	1.1	Fever/Chills	1.2	0.5
Urinary Frequency	2.5	2.2	<b>RESPIRATORY</b>		
Urinary Retention	1.9	2.2	Upper Respiratory Complaints	5.0	11.4
<b>MUSCULOSKELETAL</b>			<b>SPECIAL SENSES</b>		
Arthritis	3.1	2.7	Auditory Disturbance	5.3	3.2
<b>NEUROLOGICAL</b>			Blurred Vision	14.6	10.3
Akathisia	1.5	1.1	Gustatory Disturbance	3.1	1.1
Akinesia/Bradykinesia	8.0	8.6			
Cutaneous Temperature Disturbance	1.9	1.6			

\*Events reported by at least 1% of Wellbutrin patients are included.

**Other events observed during the entire pre-approval evaluation of Wellbutrin:** During its pre-approval assessment, Wellbutrin was evaluated in almost 2400 subjects. The conditions and duration of exposure to Wellbutrin varied greatly and a substantial proportion of the experience was gained in open and uncontrolled clinical settings. During this experience, numerous adverse events were reported; however, without appropriate controls, it is impossible to determine with certainty which events were or were not caused by Wellbutrin. The following enumeration is organized by organ system and describes events in terms of their relative frequency of reporting in the data base. Events of major clinical importance are also described in the WARNINGS and PRECAUTIONS sections of the labeling.

The following definitions of frequency are used: Frequent adverse events are defined as those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to 1/1000 patients, while rare events are those occurring in less than 1/1000 patients.

**Cardiovascular:** Frequent was edema; infrequent were chest pain, EKG abnormalities (premature beats and nonspecific ST-T changes), and shortness of breath/dyspnea; and rare were pallor and phlebitis.

**Dermatologic:** Frequent were nonspecific rashes; infrequent were alopecia and dry skin; rare were change in hair color and hirsutism.

**Endocrine:** Infrequent was gynecomastia; rare were glycosuria and hormone level change.

**Gastrointestinal:** Infrequent were dysphagia, thirst disturbance, and liver damage/jaundice; rare were rectal complaints, colitis, G.I. bleeding, and intestinal perforation.

**Genitourinary:** Frequent was nocturia; infrequent were vaginal irritation, testicular swelling, urinary tract infection, painful erection, and retarded ejaculation; rare were dysuria, enuresis, urinary incontinence, menopause, ovarian disorder, pelvic infection, cystitis, dyspareunia, and painful ejaculation.

**Hematologic/Oncologic:** Rare was lymphadenopathy.

**Neurological:** (see WARNINGS) Frequent were ataxia/incoordination, seizure, myoclonus, dyskinesia, and dystonia; infrequent were mydriasis, vertigo, and dysarthria; and rare were EEG abnormality, abnormal neurological exam, impaired attention, and sciatica.

**Neuropsychiatric:** (see PRECAUTIONS) Frequent were mania/hypomania, increased libido, hallucinations, decrease in sexual function, and depression; infrequent were memory impairment, depersonalization, psychosis, dysphoria, mood instability, paranoia, formal thought disorder, and frigidity; rare was suicidal ideation.

**Oral Complaints:** Frequent was stomatitis; infrequent were toothache, bruxism, gum irritation, and oral edema; rare was glossitis.

**Respiratory:** Infrequent were bronchitis and shortness of breath/dyspnea; rare were epistaxis and rate or rhythm disorder.

**Special Senses:** Infrequent was visual disturbance; rare was diplopia.

**Nonspecific:** Frequent were flu-like symptoms; infrequent was nonspecific pain; rare were body odor, surgically related pain, infection, medication reaction and overdose.

**Post-Approval Reports:** The following additional events were rarely observed (less than 1/1000 patients) post-approval.

**Cardiovascular:** Flushing and myocardial infarction.

**Dermatologic:** Acne.

**Gastrointestinal:** Stomach ulcer.

**Hematologic/Oncologic:** Anemia and pancytopenia.

**Neurological:** Aphasia.

**Musculoskeletal:** Musculoskeletal chest pain.

**Respiratory:** Pneumonia and pulmonary embolism.

#### OVERDOSAGE:

**Human overdose experience:** There has been limited clinical experience with overdosage of Wellbutrin. Thirteen overdoses occurred during clinical trials. Twelve patients ingested 850 to 4200 mg and recovered without significant sequelae. Another patient who ingested 9000 mg of Wellbutrin and 300 mg of tranylcypromine experienced a grand mal seizure and recovered without further sequelae.

#### DOSAGE AND ADMINISTRATION:

**General Dosing Considerations:** It is particularly important to administer Wellbutrin in a manner most likely to minimize the risk of seizure (see WARNINGS). Increases in dose should not exceed 100 mg/day in a 3 day period. Gradual escalation in dosage is also important if agitation, motor restlessness, and insomnia, often seen during the initial days of treatment, are to be minimized. If necessary, these effects may be managed by temporary reduction of dose or the short-term administration of an intermediate to long-acting sedative hypnotic. A sedative hypnotic usually is not required beyond the first week of treatment. Insomnia may also be minimized by avoiding bedtime doses. If distressing, untoward effects supervene, dose escalation should be stopped.

No single dose of Wellbutrin should exceed 150 mg. Wellbutrin should be administered t.i.d., preferably with at least 6 hours between successive doses.

**Usual Dosage for Adults:** The usual adult dose is 300 mg/day, given t.i.d. Dosing should begin at 200 mg/day, given as 100 mg b.i.d. Based on clinical response, this dose may be increased to 300 mg/day, given as 100 mg t.i.d., no sooner than 3 days after beginning therapy (see table below).

Treatment Day	Total Daily Dose	Tablet Strength	Dosing Regimen Number of Tablets		
			Morning	Midday	Evening
1	200 mg	100 mg	1	0	1
4	300 mg	100 mg	1	1	1

**Increasing the Dosage Above 300 mg/Day:** As with other antidepressants, the full antidepressant effect of Wellbutrin may not be evident until 4 weeks of treatment or longer. An increase in dosage, up to a maximum of 450 mg/day, given in divided doses of not more than 150 mg each, may be considered for patients in whom no clinical improvement is noted after several weeks of treatment at 300 mg/day. Dosing above 300 mg/day may be accomplished using the 75 or 100 mg tablets. The 100 mg tablet must be administered q.i.d. with at least 4 hours between successive doses, in order not to exceed the limit of 150 mg in a single dose. Wellbutrin should be discontinued in patients who do not demonstrate an adequate response after an appropriate period of treatment at 450 mg/day.

**Elderly Patients:** In general, older patients are known to metabolize drugs more slowly and to be more sensitive to the anticholinergic, sedative, and cardiovascular side effects of antidepressant drugs.

**References:** 1. Mendels J, Amin MM, Chouinard G, et al. A comparative study of bupropion and amitriptyline in depressed outpatients. *J Clin Psychiatry*. 1983;44(5, sec 2):118-120. 2. Wenger TL, Cohn JB, Bustrack J. Comparison of the effects of bupropion and amitriptyline on cardiac conduction in depressed patients. *J Clin Psychiatry*. 1983;44(5, sec 2):174-175. 3. Farid FF, Wenger TL, Tsai SY, et al. Use of bupropion in patients who exhibit orthostatic hypotension on tricyclic antidepressants. *J Clin Psychiatry*. 1983;44(5, sec 2):170-173. 4. Data on file, Burroughs Wellcome Co.

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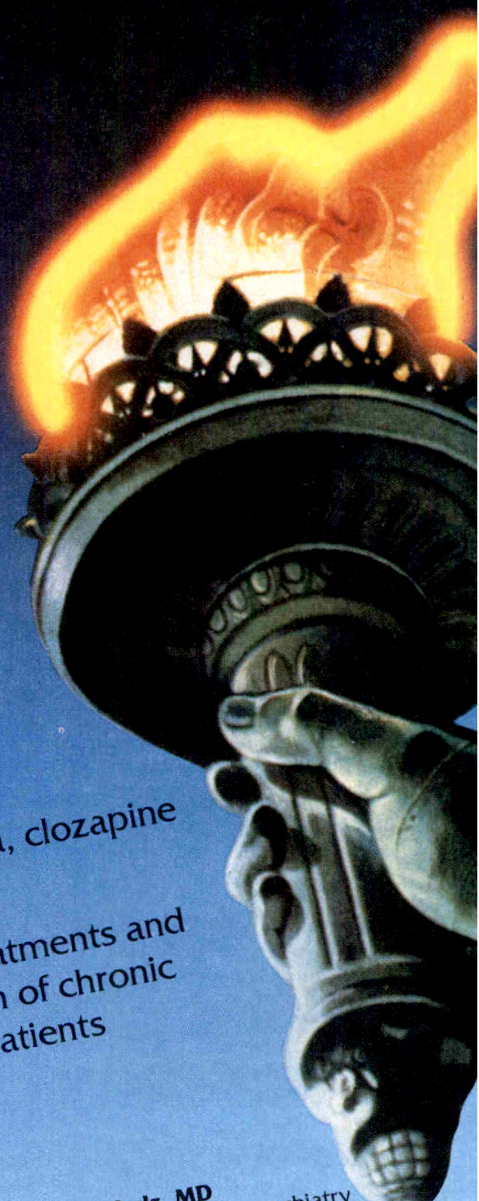
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TABLETS

**CAUTION:** Federal law prohibits dispensing without a prescription.

#### CONTRAINDICATIONS

CLOZARIL is contraindicated in patients with myeloproliferative disorders, or a history of CLOZARIL-induced agranulocytosis or severe granulocytopenia. CLOZARIL should not be used simultaneously with other agents having a well-known potential to suppress bone marrow function. As with more typical antipsychotic drugs, CLOZARIL is contraindicated in severe central nervous system depression or comatose states from any cause.

#### WARNINGS

##### General

BECAUSE OF THE SIGNIFICANT RISK OF AGRANULOCYTOSIS, A POTENTIALLY LIFE-THREATENING ADVERSE EVENT (SEE BELOW), CLOZARIL SHOULD BE RESERVED FOR USE IN THE TREATMENT OF SEVERELY ILL SCHIZOPHRENIC PATIENTS WHO FAIL TO SHOW AN ACCEPTABLE RESPONSE TO ADEQUATE COURSES OF STANDARD ANTIPSYCHOTIC DRUG TREATMENT, EITHER BECAUSE OF INSUFFICIENT EFFECTIVENESS OR THE INABILITY TO ACHIEVE AN EFFECTIVE DOSE DUE TO INTOLERABLE ADVERSE EFFECTS FROM THOSE DRUGS. CONSEQUENTLY, BEFORE INITIATING TREATMENT WITH CLOZARIL, IT IS STRONGLY RECOMMENDED THAT A PATIENT BE GIVEN AT LEAST TWO TRIALS, EACH WITH A DIFFERENT STANDARD ANTIPSYCHOTIC DRUG PRODUCT, AT AN ADEQUATE DOSE AND FOR AN ADEQUATE DURATION.

PATIENTS WHO ARE BEING TREATED WITH CLOZARIL MUST HAVE A BASELINE WHITE BLOOD CELL (WBC) AND DIFFERENTIAL COUNT BEFORE INITIATION OF TREATMENT, AND A WBC COUNT EVERY WEEK THROUGHOUT TREATMENT, AND FOR FOUR WEEKS AFTER THE DISCONTINUATION OF CLOZARIL.

CLOZARIL IS AVAILABLE ONLY THROUGH THE CLOZARIL PATIENT MANAGEMENT SYSTEM<sup>SM</sup> (CPMS<sup>SM</sup>).

##### Agranulocytosis

Agranulocytosis, defined as a granulocyte count (polys + bands) of less than 500 per mm<sup>3</sup>, has been estimated to occur in association with CLOZARIL use at a cumulative incidence at one year of approximately 1.3%, based on the occurrence of 15 U.S. cases out of 1743 patients exposed to CLOZARIL during its clinical testing prior to domestic marketing. All of these cases occurred at a time when the need for close monitoring of WBC counts was already recognized. This reaction could prove fatal if not detected early and therapy interrupted. While no fatalities have been associated with the U.S. agranulocytosis cases, and all cases have recovered fully, the U.S. sample is too small to reliably estimate the case fatality rate. Of the 112 cases of agranulocytosis reported worldwide in association with CLOZARIL use as of December 31, 1986, 35% were fatal. However, few of these deaths occurred since 1977, at which time the knowledge of CLOZARIL-induced agranulocytosis became more widespread, and close monitoring of WBC counts more widely practiced. Nevertheless, it is unknown at present what the case fatality rate will be for CLOZARIL-induced agranulocytosis, despite strict adherence to the recommendation for weekly monitoring of WBC counts.

Treatment should not be initiated if the WBC count is less than 3500 per mm<sup>3</sup>, or if the patient has a history of a myeloproliferative disorder, or previous CLOZARIL-induced agranulocytosis or granulocytopenia. Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat or any other signs of infection. If, after the initiation of treatment, the total WBC count has dropped below 3500 per mm<sup>3</sup> or it has dropped by a substantial amount from baseline, even if the count is above 3500 per mm<sup>3</sup>, or if immature forms are present, a repeat WBC count and a differential count should be done. If subsequent WBC counts and the differential count reveal a total WBC count between 3000 and 3500 per mm<sup>3</sup> and a granulocyte count above 1500 per mm<sup>3</sup>, twice weekly WBC counts and differential counts should be performed.

If the total WBC count falls below 3000 per mm<sup>3</sup> or the granulocyte count below 1500 per mm<sup>3</sup>, CLOZARIL therapy should be interrupted and patients should be carefully monitored for flu-like symptoms or other symptoms suggestive of infection. CLOZARIL therapy may be resumed if no symptoms of infection develop, and if the total WBC count returns to levels above 3000 per mm<sup>3</sup> and the granulocyte count returns to levels above 1500 per mm<sup>3</sup>. However, in this event, twice-weekly WBC counts and differential counts should continue until total WBC counts return to levels above 3500 per mm<sup>3</sup>.

If the total WBC count falls below 2000 per mm<sup>3</sup> or the granulocyte count falls below 1000 per mm<sup>3</sup>, bone marrow aspiration should be considered to ascertain granulopoietic status. Protective isolation with close observation may be indicated if granulopoiesis is determined to be deficient. Should evidence of infection develop, the patient should have appropriate cultures performed and an appropriate antibiotic regimen instituted.

Patients whose total WBC counts fall below 2000 per mm<sup>3</sup> or granulocyte counts below 1000 per mm<sup>3</sup> during CLOZARIL therapy should *not* be re-challenged with CLOZARIL. Patients discontinued from CLOZARIL therapy due to significant WBC suppression have been found to develop agranulocytosis upon re-challenge, often with a shorter latency on re-exposure. To reduce the chances of re-challenge occurring in patients who have experienced significant bone marrow suppression during CLOZARIL therapy, a single, national master file will be maintained confidentially within the CPMS (Clozaril Patient Management System).

Except for evidence of significant bone marrow suppression during initial CLOZARIL therapy, there are no established risk factors, based on worldwide experience, for the development of agranulocytosis in association with CLOZARIL use. However, a disproportionate number of the U.S. cases of agranulocytosis occurred in patients of Jewish background compared to the overall proportion of such patients exposed during the domestic development of CLOZARIL. Most of the U.S. cases occurred within 4-10 weeks of exposure, but neither dose nor duration is a reliable predictor of this problem. No patient characteristics have been clearly linked to the development of agranulocytosis in association with CLOZARIL use, but agranulocytosis associated with other antipsychotic drugs has been reported to occur with a greater frequency in women, the elderly and in patients who are cachectic or have serious underlying medical illness; such patients may also be at particular risk with CLOZARIL.

To reduce the risk of agranulocytosis developing undetected, CLOZARIL will be dispensed only within the Clozaril Patient Management System.

##### Seizures

Seizure has been estimated to occur in association with CLOZARIL use at a cumulative incidence at one year of approximately 5%, based on the occurrence of one or more seizures in 61 of 1743 patients exposed to CLOZARIL during its clinical testing prior to domestic marketing (i.e., a crude rate of 3.5%). Dose appears to be an important predictor of seizure, with a greater likelihood of seizure at the higher CLOZARIL doses used.

Caution should be used in administering CLOZARIL to patients having a history of seizures or other predisposing factors. Because of the substantial risk of seizure associated with CLOZARIL use, patients should be advised not to engage in any activity where sudden loss of consciousness could cause serious risk to themselves or others, e.g., the operation of complex machinery, driving an automobile, swimming, climbing, etc.

##### Adverse Cardiovascular Effects

Orthostatic hypotension can occur with CLOZARIL treatment, especially during initial titration in association with rapid dose escalation, and may represent a continuing risk in some patients. Tachycardia, which may be sustained, has also been observed in approximately 25% of patients taking CLOZARIL, with patients having an average increase in pulse rate of 10-15 bpm. The sustained tachycardia is not simply a reflex response to hypotension, and is present in all positions monitored. Either tachycardia or hypotension may pose a serious risk for an individual with compromised cardiovascular function. A minority of CLOZARIL-treated patients experience ECG repolarization changes similar to those seen with other antipsychotic drugs, including S-T segment depression and flattening or inversion of T waves, which all normalize after discontinuation of CLOZARIL. The clinical significance of these changes is unclear. However, in clinical trials with CLOZARIL, several patients experienced significant cardiac events, including ischemic changes, myocardial infarction, nonfatal arrhythmias and sudden unexplained death. Causality assessment was difficult in many of these cases because of serious preexisting cardiac disease and plausible alternative causes. Rare instances of sudden, unexplained death have been reported in psychiatric patients, with or without associated antipsychotic drug treatment, and the relationship of these events to antipsychotic drug use is unknown. CLOZARIL should be used with caution in patients with known cardiovascular disease, and the recommendation for gradual titration of dose should be carefully observed.

##### Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). No cases of NMS have been attributed to CLOZARIL alone. However, there have been several reported cases of NMS in patients treated concomitantly with lithium or other CNS-active agents.

##### Tardive Dyskinesia

A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of treatment, which patients are likely to develop the syndrome.

There are several reasons for predicting that CLOZARIL may be different from other antipsychotic drugs in its potential for inducing tardive dyskinesia, including the preclinical finding that it has a relatively weak dopamine blocking effect and the clinical finding of a virtual absence of certain acute extrapyramidal symptoms, e.g., dystonia. In addition, there have been no confirmed cases of tardive dyskinesia developing in association with CLOZARIL use. Nevertheless, it cannot yet be concluded, without more extended experience, that CLOZARIL is incapable of inducing this syndrome.

##### PRECAUTIONS

Because of the significant risk of agranulocytosis and seizure, both of which present a continuing risk over time, the extended treatment of patients failing to show an acceptable level of clinical response should ordinarily be avoided. In addition, the need for continuing treatment in patients exhibiting beneficial clinical responses should be periodically re-evaluated. During CLOZARIL therapy, patients may experience transient temperature elevations above 100.4°F (38°C), with the peak incidence within the first three weeks of treatment. While this fever is generally benign and self-limiting, it may necessitate discontinuing patients from treatment. On occasion, there may be an associated increase or decrease in WBC count. Patients with fever should be carefully evaluated to rule out the possibility of an underlying infectious process or the development of agranulocytosis. In the presence of high fever, the possibility of neuroleptic malignant syndrome (NMS) must be considered. CLOZARIL has very potent anticholinergic effects, and great care should be exercised in using this drug in the presence of prostatic enlargement or narrow angle glaucoma. Because of initial sedation, CLOZARIL may impair mental and/or physical abilities, especially during the first few days of therapy. The recommendations for gradual dose escalation should be carefully adhered to, and patients cautioned about activities requiring alertness. Clinical experience with CLOZARIL in patients with concomitant systemic diseases is limited. Nevertheless, caution is advisable in using CLOZARIL in patients with hepatic, renal or cardiac disease.

##### Information for Patients

Patients who are to receive CLOZARIL should be warned about the significant risk of developing agranulocytosis. They should be informed that weekly blood tests are required to monitor for the occurrence of agranulocytosis, and that CLOZARIL tablets will be made available only through a special program designed to ensure the required blood monitoring. Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat, malaise, mucous membrane ulceration or other possible signs of infection. Particular attention should be paid to any flu-like complaints or other symptoms that might suggest infection. Patients should be informed of the significant risk of seizure during CLOZARIL treatment, and they should be advised to avoid driving and any other potentially hazardous activity while taking CLOZARIL. Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration. Patients should notify their physician if they are taking, or plan to take, any prescription or over-the-counter drugs or alcohol. Patients should notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should not breast feed an infant if they are taking CLOZARIL.

**CLOZARIL<sup>®</sup>**

(clozapine)

TABLETS

**Drug Interactions**

The risks of using CLOZARIL in combination with other drugs have not been systematically evaluated. The mechanism of CLOZARIL-induced agranulocytosis is unknown; nonetheless, the possibility that causative factors may interact synergistically to increase the risk and/or severity of bone marrow suppression warrants consideration. Therefore, CLOZARIL should not be used with other agents having a well-known potential to suppress bone marrow function. Given the primary CNS effects of CLOZARIL, caution is advised in using it concomitantly with other CNS-active drugs. Because CLOZARIL is highly bound to serum protein, the administration of CLOZARIL to a patient taking another drug which is highly bound to protein (e.g., warfarin, digoxin) may cause an increase in plasma concentrations of these drugs, potentially resulting in adverse effects. Conversely, adverse effects may result from displacement of protein-bound CLOZARIL by other highly bound drugs.

**CLOZARIL may also potentiate the hypotensive effects of antihypertensive drugs and the anticholinergic effects of atropine-type drugs. The administration of epinephrine should be avoided in the treatment of drug-induced hypotension because of a possible reverse epinephrine effect.**

**Pregnancy Category B**

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, and in view of the desirability of keeping the administration of all drugs to a minimum during pregnancy, this drug should be used only if clearly needed.

**ADVERSE REACTIONS**

Adverse events observed in association with the use of CLOZARIL in clinical trials at an incidence of 5% or greater were: central nervous system complaints, including drowsiness/sedation, dizziness/vertigo, headache and tremor; autonomic nervous system complaints, including salivation, sweating, dry mouth and visual disturbances; cardiovascular findings, including tachycardia, hypotension and syncope; and gastrointestinal complaints, including constipation and nausea; and fever. Complaints of drowsiness/sedation tend to subside with continued therapy or dose reduction. Salivation may be profuse, especially during sleep, but may be diminished with dose reduction.

**DOSAGE AND ADMINISTRATION****Initial Treatment**

It is recommended that treatment with CLOZARIL begin at 25 mg once or twice daily, and then be continued with daily dosage increments of 25 to 50 mg/day, if well-tolerated, to achieve a target dose of 300 to 450 mg/day by the end of two weeks. Subsequent dosage increments should be made no more than once- or twice-weekly, in increments not to exceed 100 mg. Cautious titration and a divided dosage schedule are necessary to minimize the risks of hypotension, seizure, and sedation.

**Therapeutic Dose Adjustment**

Daily dosing should continue on a divided basis as an effective and tolerable dose level is sought. While many patients may respond adequately at doses between 300-600 mg/day, it may be necessary to raise the dose to the 600-900 mg/day range to obtain an acceptable response. [Note: In the multicenter study providing the primary support for the superiority of CLOZARIL in treatment resistant patients, the mean and median CLOZARIL doses were both approximately 600 mg/day.]

Because of the possibility of increased adverse reactions at higher doses, particularly seizures, patients should ordinarily be given adequate time to respond to a given dose level before escalation to a higher dose is contemplated.

Dosing should not exceed 900 mg/day.

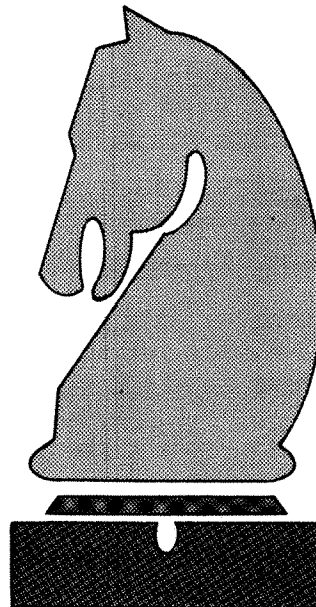
**Discontinuation of Treatment**

In the event of planned termination of CLOZARIL therapy, gradual reduction in dose is recommended over a 1 to 2 week period. However, should a patient's medical condition require abrupt discontinuation (e.g., leukopenia), the patient should be carefully observed for the recurrence of psychotic symptoms.

**CLOZARIL is available only through the Clozaril Patient Management System, a program that combines white blood cell testing, patient monitoring, pharmacy, and drug distribution services, all linked to compliance with required safety monitoring.**

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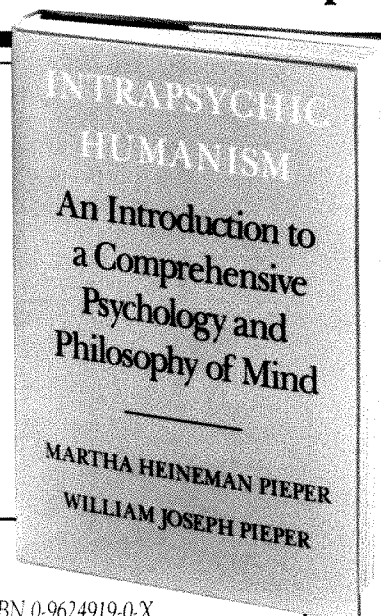
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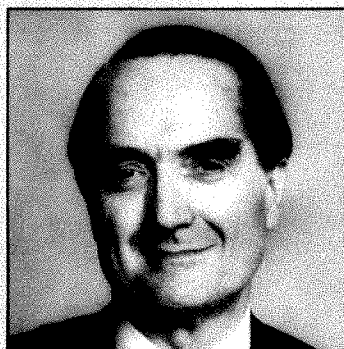


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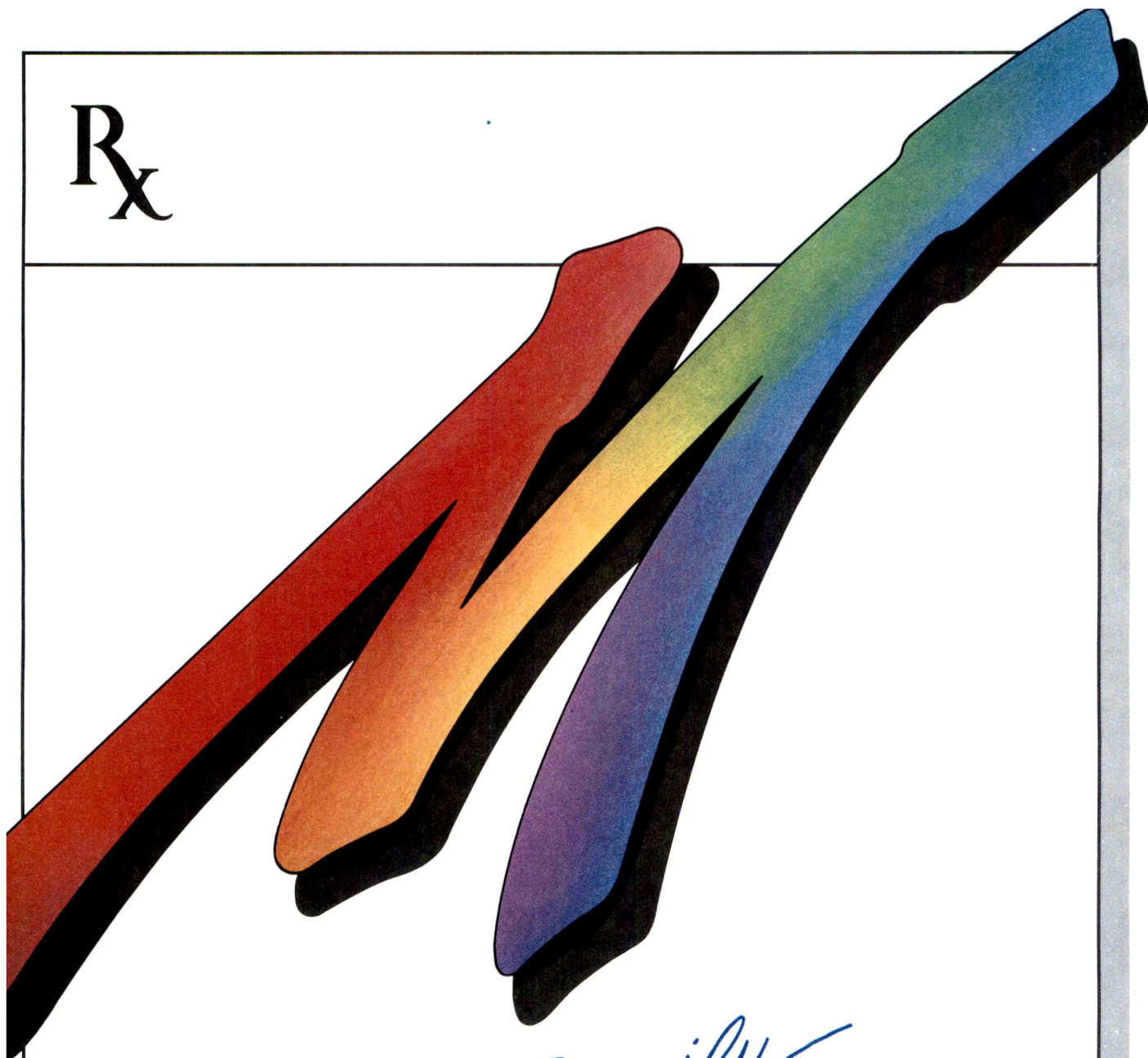
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MARTHA HEINEMAN PIEPER and WILLIAM JOSEPH PIEPER are in private practice in Chicago. Martha Heineman Pieper, Ph.D., is currently adjunct professor at Smith College School for Social Work and has published numerous articles, particularly on the philosophy of research. William Joseph Pieper, M.D., has served on the Child Therapy Faculty of the Chicago Institute for Psychoanalysis and is clinical associate professor of psychiatry at Rush Presbyterian-St. Lukes Medical School.



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## *Special Articles*

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### Cults and Zealous Self-Help Movements: A Psychiatric Perspective

Marc Galanter, M.D.

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*Modern cults and zealous self-help movements exercise an intense group influence and can have a major impact on their members' psychiatric status. On the basis of research findings, the author describes the charismatic group, a generic model for such cohesive, intensely ideological movements. He examines the psychological forces they tap and the way they can both relieve and exacerbate psychopathology. The model is then used to explain the operation of zealous self-help programs that address psychiatric syndromes; these are directed at problems of the medically ill, substance abusers, and relatives of psychiatric patients.*

(Am J Psychiatry 1990; 147:543-551)

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In recent decades, psychiatrists and other mental health professionals have encountered a variety of ideologically oriented zealous groups of diverse character and goals. Some, like the Unification Church ("Moonies"), are cults or new religious movements (1, 2). Others, like Alcoholics Anonymous (AA), are lay organizations that rely on peers to help fellow members recover from the same illness. Still others are professionally directed self-help programs, like the drug treatment therapeutic communities. Although these groups are very different in their character and their impact on members, there are similarities among them that help explain how they exert their considerable

influence on members' psychiatric status. In this paper, I will clarify these similarities by developing the model of the charismatic group. I will then use this model to explain the psychiatric impact of certain self-help programs that impinge on clinical practice.

#### DEFINITIONS

The model of the charismatic group (3, 4) can be used generically to describe modern cults and zealous self-help movements. Such a group is characterized by 1) a high level of social cohesiveness, 2) an intensely held belief system, and 3) a profound influence on its members' behavior. It is "charismatic" because of the commitment of members to a fervently espoused, transcendent goal; indeed, this goal is frequently articulated by a charismatic leader or ascribed to the progenitor of the group. Charismatic groups can relieve certain symptoms associated with psychopathology, but they can precipitate psychiatric symptoms as well.

Among zealous groups, the concept of a cult is more specifically religious. It connotes deviance from established belief and, often, transcendental experiences (5). Some modern religious cults have been called new religious movements by writers who are attentive to the potential of cults for finding a place in the religious mainstream (1, 2). Those cultic groups which conform to the definition of the charismatic group will be discussed here.

A self-help group is a voluntary program that operates to promote mutual aid among its members (6). Some self-help groups provide matter-of-fact advice and information without the intense commitment of participants, but others can be highly zealous and ideological in nature. I will consider the latter type of self-

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Received Aug. 5, 1988; revision received June 29, 1989; accepted Aug. 25, 1989. From the Division of Alcoholism and Drug Abuse, Department of Psychiatry, New York University School of Medicine. Address reprint requests to Dr. Galanter, Division of Alcoholism and Drug Abuse, Department of Psychiatry, New York University School of Medicine, 550 First Ave., New York, NY 10016.

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help groups here because they too conform to the model developed in this paper.

### THE NATURE OF THE CHARISMATIC GROUP

An examination of modern cultic groups in the West, augmented by related cross-cultural examples, can help to explain the psychiatric impact of the charismatic group. It will also serve as a basis for studying modern self-help groups that influence their members in a similar fashion and may have a direct impact on prevention and rehabilitation of psychiatric illness.

Groups such as the Unification Church, the Divine Light Mission, Hare Krishna, and the Children of God are not without precedent. History reveals many examples of such deviant movements, most often appearing when a society does not address certain fundamental social problems (7); in this respect they parallel zealous healing movements that arise when potential members feel that their medical needs have not been properly addressed.

#### *Psychological Forces in the Group*

To understand how charismatic groups can profoundly shape the thinking and behavior of their members I will consider the psychological forces they bring to bear on the preexisting disposition and psychology of recruits. One of these forces, group cohesiveness, is defined as the product of all the forces that act on members to keep them engaged in a group (8). When cohesiveness is strong, participants work to sustain the commitment of their fellow members, to protect them from threat, and to ensure the safety of shared resources. This can lead, as Pattison (9) and others (4, 10, 11) have pointed out, to the members' psychotherapeutic benefit.

The impact of group cohesiveness on the psychological status of members was evident in a study of a modern charismatic sect, the Divine Light Mission (3, 12). Young adult members of the group reported appreciable psychiatric problems before joining. For example, 30% had sought professional help and 9% had been hospitalized for emotional disorders. Furthermore, their self-reports reflected a considerable relief in neurotic distress after they became affiliated with the Divine Light Mission. Their responses also demonstrated an intense social cohesiveness in the group that was highly correlated with the degree of symptom relief evidenced by individual members. Cohesive forces based on family and community ties operate in a similar fashion in a wide variety of indigenous mental healing rituals, both in preindustrial societies, as in Zar ceremonies of Northeast Africa (13), and in the United States, as in *Espiritismo* among Puerto Rican immigrants (14).

Shared belief, a second force in the charismatic group, was evident in studies on the psychological well-being of longstanding Unification Church mem-

bers (15). Measures of social cohesiveness and religious belief accounted for a large portion of the variance in well-being, and items that measured religious belief were the highest ranking predictors of well-being. This suggests the additional role of belief as a force in charismatic groups. It also reflects the importance of a set of beliefs held by healers and their patients about illness and treatment. Kleinman and Gale (16) found this explanatory model to be an important component of the effectiveness of indigenous healing in their cross-cultural studies of shamanistic treatment.

Altered consciousness is another force operating in the charismatic group. It is frequently described by modern cult members (1, 2) and is typically elicited in an intense group experience. As pointed out by Proudfoot and Shaver (17), in relation to religious conversion, altered consciousness can serve as the basis for the converts' attributing a new construction of reality to their life. In Divine Light Mission and Unification Church samples (12, 15), for example, my associates and I found that experiences of altered consciousness were significantly correlated with the improved affective status experienced by members on conversion. There are also parallels to the ceremonies of indigenous mental healers (18): descriptions date back half a century to the observations of Leighton and Leighton (19) among Navajo shamans. Emetics and even hot poker were used by Navajos to induce transcendent states during rites for treatment of major mental illnesses (20).

In the charismatic group, the forces of group cohesiveness, shared belief, and altered consciousness operate to compel behavioral conformity and modulate affect without overt coercion. To understand this process of social control, it is useful to contrast it with the influence of brainwashing. Brainwashing was described by Lifton (21) among prisoners of the Korean War who were forcibly confined by the Communist Chinese. In both brainwashing and charismatic groups, those directing the process maintain control over the "context of communication" in order to prevent the expression of perspectives contrary to their own. In the brainwashing setting, however, participants are imprisoned and physically coerced. There is no physical coercion in charismatic groups. Instead, the psychological forces described above allow members to attribute new meaning and values to their experiences by means of social reinforcement of compliance.

How does this reinforcement take place? Findings on the role of these forces (3, 4, 10, 22) suggest the operation of a "relief effect" in the psychiatric impact of charismatic groups. That is to say, both recruits and long-term members experience a relief from emotional distress when they feel more closely affiliated with the group; a decline in affiliate feelings, on the other hand, can result in greater distress. Such an effect, sociobiologically grounded (3) and mediated by the social context, can serve as an operant reinforcer for regulating behavior (23). Members who act in accordance with the group's expectations are reinforced by enhanced

well-being; when they reject the group's behavioral norms they experience the negative reinforcement of increased distress. This also serves to enhance the likelihood of members' maintaining affiliation with the group and compliance with its expectations for behavior. It takes place both informally and in structured rituals. In AA, a modern healing group, for example, Rodin (24) pointed out that members' compliance is regularly reinforced by their peers at meetings. This is done by means of the verbal expressions of approval and demonstrations of affection routinely made by members to reward speakers during a chapter meeting.

Since the operant reinforcement of approved behaviors can engage members into compliance with the group and restructure their perceptions of the world around them as well, it can also serve as the basis for a remission in recruits' pathological perceptions. The enhanced well-being inherent in the affiliation process can then contribute to the relief of major psychopathology, as illustrated by the following case history.

*Case 1.* A 24-year-old technician with no history of psychiatric illness became increasingly isolated over the course of a year after beginning to smoke marijuana. He felt that his co-workers were conspiring to have him arrested for drug possession. He then moved into a secluded rural setting, where he soon came to believe that his "soul was moving out" of him and that he saw flying saucers nearby. Soon he felt he was going out of his mind. At this point he met several members of an Eastern cultic group, who invited him to spend time at their communal residence. After 2 months of meditation and daily attendance at their religious services he was no longer anxious or delusional, reporting that he was "at peace with himself." A year later, he had had no recurrence in symptoms and was still involved in the group's activities. His *DSM-III-R* diagnosis was delusional disorder, persecutory type (297.10).

The intense cohesiveness of the charismatic group in combination with its ability to influence members' beliefs can yield relief in psychopathology. It can also generate psychiatric syndromes, however. This is particularly true when an individual becomes alienated from a cohesive group but still accepts its belief system. The potent impact of such estrangement, even to the point of inducing psychotic symptoms, is illustrated below.

*Case 2.* A 16-year-old boy whose family belonged to a neo-Christian cult was admitted to the hospital because he was hearing voices. Both the patient and others reported that he had never experienced psychiatric difficulties until fellow members caught him smoking marijuana; the members insisted that he was tainted by the Devil because he had violated the group's religious injunction against smoking marijuana. Very soon after this experience, the boy became alienated from the group and ran off to stay at the home of a relative not affiliated with the cult. Over the course of a month he became increasingly guilty and anxious about having left the group and then began to hallucinate the voice of the Devil telling him he had betrayed the cult. His symptoms remitted during a 1-month hospitalization that provided sup-

portive milieu treatment only. His *DSM-III-R* diagnosis was brief reactive psychosis (298.80).

### *The Experience of Membership*

The impact of group forces is felt at each stage of membership in a charismatic group, from induction to stabilization to departure. A description of the course of membership in the Unification Church will illustrate the operation of these psychological forces.

One recruitment format used by the Unification Church is the structured workshop series. In studying this recruitment setting (25), I found that a sizable portion of participants (29%) agreed to stay beyond the weekend for which they were initially invited and that 9% joined after the entire 3-week experience. Analysis of self-report data revealed that those who stayed beyond the first weekend—even those who did not later join—had become highly involved in the group process. This occurred both on the level of social cohesiveness and in terms of accepting the group's creed. Those who later joined the group, however, were experiencing greater psychological distress before the workshops and felt less cohesive ties to friends and family outside the group. This suggests that persons who demonstrate a modicum of interest in a charismatic group can easily become engaged on interpersonal and cognitive levels. Long-term engagement, however, may require the fertile soil of psychological distress and alienation.

Once a person joins a charismatic group, his or her behavior is typically subject to its control. This was evident in the marked decline in heavy drug and alcohol use effected by the Unification Church in its recruits, which continued in long-term members (15). It was also illustrated by the nature of the engagement (26) and marriage rituals (27) of the Unification Church, since the norms espoused in these rituals deviated greatly from those of the U.S. middle class. For example, Reverend Moon himself selected the mates for almost all Church members. A large majority of Unification Church fiancés and fiancées (87%) reported that they felt no preference at all for a particular individual at the time Moon chose their mate for them, reflecting their compliance on a cognitive level. The affective impact of the aforementioned "relief effect" was evident in the distress associated with non-compliance; those contemplating severing their engagement were the most severely depressed subgroup of members.

In a 3-year follow-up study of the engaged members, despite the remarkably deviant nature of the cult's marital customs, almost all (95%) were still active in the Unification Church and were married to fellow Church members (88%). The members' commitment could be understood by recourse to the model of the pincer effect: on the one hand, the Church, like other charismatic groups, created distress by ordering deviant behaviors; on the other hand, it provided relief

when members complied and maintained their commitment to the group.

Members' commitment to a charismatic group is remarkably persistent, even after they leave the group. For example, 3 years after their departure from the Unification Church, ex-members still maintained a considerable fidelity toward the group, although most of them were well adjusted in the general community (28). A sizable majority still cared strongly for the members they knew best and reported that they "got some positive things" out of their involvement with the group. This fidelity is evidence of the potential of a charismatic group for continuing its influence even after a member departs, as we shall see among self-help groups who operate along similar lines.

It is useful to consider how charismatic groups operate as social systems in order to understand why they elicit certain puzzling behaviors in their members. As members become part of the social system of the group, they become entrained in the system's need to assure its own stability. The behavior of individuals, which may appear pathological, may reflect no more than responses induced in the group to assure its integrity. For example, one function of social systems is boundary control—protection from external disruptions. Such self-protectiveness is frequently seen in charismatic groups, often to the point of paranoia. It was evident in my findings on the Divine Light Mission (3), where the single item that correlated most highly with improvement in a member's neurotic distress on joining was suspiciousness of outsiders; outsiders might undermine a recruit's commitment to the group. Similarly, a cult may implicitly suggest that members close themselves off from any outsider's influence. Because of this, some members may even manifest behavior something like dissociative phenomena when they feel that they are vulnerable. This is evident in the affective constriction and stereotyped behavior that Clark (29) and Singer (30) described as possibly meeting criteria for a dissociative disorder.

## ZEALOUS SELF-HELP MOVEMENTS

Some 12 million people in the United States now belong to self-help organizations, a figure that has doubled in the last 12 years (31). An appreciable portion of these individuals have joined zealous groups that address psychiatric problems ranging from kleptomania to schizophrenia. A perspective on charismatic groups can help explain more explicitly how zealous self-help movements achieve their clinical impact by means of psychotherapeutic factors often described as nonspecific (32). These nonreligious charismatic groups are similar in important ways to the model described above in that they too are highly cohesive, ideologically oriented, and have a strong influence on their members' behavior. Unlike many of the new religious movements, however, they are more focused on spe-

cific issues and do not assert control over other aspects of members' lives.

Modern charismatic self-help groups are similar in their operation to many non-Western healers. Unlike modern medical treatments, both zealous self-help groups and non-Western indigenous healers generally use group rituals that engage the patient's family and other community members (18). Zealous self-help groups and indigenous healers also draw on certain aspects of their members' social and community networks. In this way they are like the social-psychiatric therapies described by Caplan (33) and the family network therapy described by Speck and Attneave (34) and Schoenfeld et al. (35). In all these examples, the cohesive forces and assumptive beliefs of a social network are used as tools in the therapeutic process.

### *Zealous Movements for Relieving Mental Illness*

Several zealous self-help movements purport to ameliorate the mental state of their members, and some may be considered charismatic groups because of their intense cohesiveness, strongly held belief systems, and the considerable influence they exert over their members' behavior. Most of these groups define their own perspective on the problems they address and disregard standard psychiatric treatment. Lieberman et al. (36) studied large samples of ideologically oriented "growth centers" and women's groups and found their goals, if not their nomenclature, to be similar to those of traditional psychotherapy.

Erhard Seminars Training (est), a highly influential and zealous self-actualization movement, illustrates many characteristics of the charismatic group. It was established by a layman in 1971 and attracted scores of thousands of persons who were well adapted with the promise of "transforming their ability to experience living." Like the Unification Church and other charismatic groups, est engaged recruits in a setting where communications were subtly controlled by longstanding members and where intense commitment to the group's worldview was promoted. Like many indigenous healing groups and modern cults, it made use of altered consciousness induced through manipulation of the social setting. This was achieved during induction workshops where participants underwent distortions in sleep, eating, and toileting patterns and were exposed to intense emotion and verbal abuse. Some psychiatrists, such as Simon (37), observed that the program provided considerable psychological benefits to members, but others, such as Glass et al. (38, 39), reported serious psychological sequelae of the intense pressure placed on conflicted recruits, not unlike the cult member described in case 2.

One example of a psychiatrically oriented self-help program is Recovery, Inc. It has 10,000 members nationwide and was founded by a psychiatrist specifically to provide members with aid in managing their symptoms. Indeed, the group acknowledges the important role of mental health professionals in treating psychi-



atric illness (40). As with inductees to other charismatic groups, recruits to Recovery encounter the program at a time of emotional distress. Also like those groups, Recovery uses a highly cohesive social setting in which members are engaged into acceptance of the cognitive system and beliefs of the program. Recovery's group meetings are designed to train members to recognize antecedents of emotional disruption and then apply formalized approaches, such as "spotting" of problematic attitudes, to avert dysphoric reactions. The ensuing process may then be likened to the aforementioned pincer effect, which enabled the Unification Church to manage the behavior of its members and aid them in buffering the impact of disruptive life events.

To examine the capacity of the charismatic group to assume some of the traditional roles of the psychiatrist, I examined the potential of the program to relieve distress and yield a diminished need for psychotropic medications and psychotherapy in a representative sample of Recovery members (41). Members' reports revealed that they had been heavy consumers of psychiatric services and that most had been hospitalized for mental illness. Over the course of Recovery membership, however, an appreciable improvement in psychiatric status was evident: the subjects reported considerably lower scores for neurotic distress after joining than before joining. Furthermore, the psychological well-being of longstanding members was no different from those of community control subjects, and fewer of them required psychotropic medications and psychotherapy than did members who had joined more recently. Importantly, as observed in studies of the Unification Church and the Divine Light Mission, strong ties to the group were significant predictors of improvement in well-being.

These findings suggest that zealous self-help programs that incorporate the charismatic group model can serve as adjuncts, even collaborators, in psychiatric care. This observation is illustrated by the following case.

*Case 3.* A 41-year-old housewife joined Recovery on the recommendation of her family physician. For several years she had experienced episodes of panic along with the fear that she would jump off a highway overpass. This led her to restrict her activities outside the home. Occasionally, when anxious, she would strike her 6-year-old daughter on minor provocation. She had refused to take alprazolam prescribed by her family physician because she was afraid of becoming addicted. She reported that at her first Recovery meeting she felt a "relief in the tension I carried around with me every day," and after 3 months she was less fearful when in the streets and stopped hitting her child. Thereafter she agreed to comply with her physician's prescriptions because, as she said, Recovery taught her to cooperate with doctors. Her diagnosis was panic disorder, with agoraphobia (300.21).

Psychiatrists' use of zealous self-help modalities such as Recovery still remains modest: only 12% of the subjects in my Recovery sample had been referred to the program by a psychiatrist. This deficit is underlined

by community-based studies (42), which have found that psychiatrists play a marginal role in efforts to promote the development of self-help groups in the health and mental health fields. Furthermore, there is only one report in the literature, by Lee (43), of an attempt to use Recovery in psychiatrically managed institutions for treatment of the mentally ill, where mobilizing patients for a positive adaptation in the community would be most valuable. Nonetheless, studies of another peer-led group, GROW (44), showed some promise for developing affiliation with established mental health systems.

### *12-Step Programs Such as AA*

A worldwide membership of more than 1.5 million (45) testifies to the ability of AA to engage alcoholics and help them change their longstanding behaviors. AA's group process suggests that its operation as a charismatic group accounts for much of this success, as evident in the psychological forces described above. For example, the 12 steps of AA recovery, central to its belief system, are zealously espoused by its members. Members are highly cohesive and meet frequently—generally daily for the first 3 months. They form a mutually protective "social cocoon" (46) and, like members of new religious movements, avoid outsiders if they threaten the group's ethos, which in this case is total abstinence.

The emergence of AA also parallels the rise of charismatic religious groups in a number of ways. Bill W, its founder, was experiencing great despair when he had a revelatory experience that was clearly religious in nature: "All at once I found myself crying out, 'If there is a God, let Him show Himself!' Suddenly the room lit up with a great white light. . . . It seemed to me in my mind's eye that I was on a mountain and that a wind, not of air, but of spirit was blowing" (47). Bill went on from this experience to preach to other alcoholics and, as with cultic groups described above, the forces of shared belief and group cohesiveness have become central in the engagement process of AA (48, 49). Furthermore, the program's evolution from these early origins to a large organization parallels the development of rituals and bureaucracy described by Max Weber for charismatic religions (4, 50).

Indigenous healers, as well, may draw on traits of the charismatic group to achieve drinking cessation. For example, the transcendent experience described by Bill W has its parallel in that of the Salish Indians of British Columbia (51), who rely on group-induced altered consciousness to treat alcohol abuse.

The Impaired Physicians Program of Georgia, developed by Talbott, is an excellent example of how the charismatic group psychology of the 12-step model of AA can be integrated into institutional care (52). The Impaired Physicians Program includes a 1-month hospitalization on an addiction treatment unit, 3 months in a community-based transitional residence, and follow-up through a network of recovering physician

monitors. All components are imbued with the AA ideology and oriented to engendering a cohesiveness among the members based on the 12-step philosophy. Since almost all addiction treatment programs in the United States now use the 12-step model developed in AA as an ideological touchstone, if not a principal modality, my associates and I studied a sample of rehabilitated physicians who were in contact with the Impaired Physicians Program an average of 3 years after discharge from residential care (53). Their responses reflected zealous espousal of the 12-step model, and they were still going to AA meetings an average of 5.6 times weekly. They ranked AA as the most influential of the modalities contributing to their recovery, more so than the transitional residence, counseling, family commitments, monitoring by their peers, and the desire to return to work. The following case history illustrates how AA beliefs can be combined with professional care to effect rehabilitation.

*Case 4.* A second-postgraduate-year resident in anesthesiology with a history of drug abuse became addicted to fentanyl, a very short-acting narcotic analgesic. He retrieved it from spent syringes in the operating room and was injecting himself up to 12 times daily. His chief of service directed him to go for treatment, but an initial trial ended in his transfer to the Impaired Physicians Program after he was found to be bringing heroin into the rehabilitation unit. Despite one episode of alcohol intoxication at the Impaired Physicians Program halfway house, he made a commitment to the 12 steps of AA supported by identification with his intensely committed fellow physicians. After 5 months in the Impaired Physicians Program he returned to his residency but soon experienced craving for narcotics in the operating room. At this point he decided to enroll in a graduate school in public health. Four years later he was still abstinent and working in a clinical administrative position; he attributed his sobriety primarily to his continuous engagement in AA, which he attended four times weekly, even after he had dropped all but limited ties to his treating physicians. His diagnosis was severe polysubstance dependence (304.90).

This case illustrates certain aspects of charismatic groups, including the role of zealous fellow "believers" in induction and the value of a structured social program for engaging recruits. A zealous self-help program like AA can be promoted by medical staff and can later serve as the primary vehicle of therapy. Case 4 also shows the continuing fidelity and conformity elicited by the group and the way it can address a focal area of pathological function.

#### *Zealous Groups for Institutional Treatment*

Zealous self-help group modalities can be used in hospitals or clinics and directed by professionals. They thereby capture some of the therapeutic potential of charismatic groups and at the same time benefit from rationally structured institutional treatment. Perhaps best known of institutionally based groups of this type are the drug-free therapeutic communities such as Phoenix House and Daytop Village. There are more

than 500 such communities in operation across the United States (54). Like the charismatic groups, these have a strongly espoused ideology—namely, that addiction is rooted in deviant attitudes and is treatable through frank and aggressive confrontation by peers. Outcomes for drug abuse and social adaptation comparable to those in patients given methadone maintenance therapy have been reported (55).

A strong ideological orientation and an intensely cohesive milieu, characteristic of a charismatic group, have also been used in the context of institutional treatment of schizophrenic patients. In reporting on Soteria House, an experimental community-based treatment program for such patients, Mosher et al. (56) underlined the importance of the program's ideological underpinnings. They pointed out that the treatment model was predicated on belief in the program philosophy derived from Laing (57)—namely, that schizophrenia is an uncommon but meaningful reaction to problems of maturation that can be worked through by intensive interpersonal exchange. Mosher and Menn (58) found that the outcomes of these patients, most of whom (82%) had been treated without neuroleptics, were comparable to those of a control group treated in a traditional hospital-based setting where neuroleptics were used for all patients. Successful outcomes with less use of psychotropic medications have parallels in other zealous treatments, such as Recovery, Inc., described above.

Using a similar rationale for drawing on self-help for institutional care, my associates and I attempted to ascertain the viability of zealous peer-led treatment for alcoholism in a hospital setting (59). We wanted to investigate the feasibility of meeting an increasing demand for care without increasing the available staff. The experimental self-help program was therefore operated with only half the professional counseling staff as the traditional control program, and day-to-day clinical management was largely placed in the hands of abstinent senior patients (supervised by staff) to encourage patients to identify with a zealous peer group. The program's ideology, strongly espoused at all patient meetings, was that alcoholics can achieve recovery by developing a community of mutual aid in the hospital-based clinic. This experimental model was effective despite the low staffing ratio. The rates of the experimental subjects for engagement into ambulatory care from the inpatient service and for social adjustment were higher than those of the control patients; the groups did not differ on other outcome variables (59). The mutual commitment among the experimental patients was much greater than is typical of institutional settings and elicited considerable efforts for mutual aid, as illustrated by case 5.

*Case 5.* One alcoholic patient who had been abstinent for 8 months came to the self-help clinic intoxicated following a crisis in his family. He reported to fellow patients that he had fallen down a staircase earlier in the day and had bruised his head. A senior patient with established sobriety who was

responsible for attending to crises brought the relapsing patient to see the alcoholism counselor and then went with him to the emergency room to seek medical evaluation. He next took him to an AA meeting of a group that the distressed patient had previously joined, enabling him to reestablish his abstinence. At his next group therapy session at the clinic, other patients offered to get together with the patient during the following week, providing encouragement and reinforcement of the group ideal of abstinence.

The potential for institutionally based zealous group programs may be greater than appreciated. In Yugoslavia, for example, Hudolin established a nationwide network of several hundred "clubs" designed to carry out aftercare for alcoholic patients (60). The ideology (or belief system) enunciated in the program is closely aligned with the country's socialist orientation, and the system is collaboratively operated by physicians and recovering patients. In a study of several of the clubs in this network (61), I found medical staff and patients participating as peers in a way that is uncommon in clinics in the United States, leading to an apparent enhanced social cohesiveness and commitment to common ideals. By such means, clearly aligned with the ideology of mutuality enunciated in the socialist state, acceptance of the shared goal of abstinence was promoted so that physicians and patients were mutually engaged in a common pursuit.

*Case 6.* In one typical club meeting, held in a factory, a physician attached to the club lectured alcoholic workers on health matters and then evaluated patients medically. After this, he participated as a peer in a meeting conducted by the club officers, themselves recovering alcoholics, to plan for a holiday that commemorated an event on the socialist calendar. The ideological significance of the holiday was discussed by participants as one important reason to maintain abstinence.

### *Self-Help for the Families of the Psychiatrically Impaired*

Families of the psychiatrically disabled have bonded together in zealous peer-led groups to relieve the symptoms of the patients' illnesses and to influence the nature of health care delivery. The National Alliance for the Mentally Ill has been highly influential in this regard. Like modern religious sects in their early phases, the National Alliance is currently undergoing a phase of aggressive recruitment. Its membership has increased about fivefold in the last 6 years (62). Its zealously held philosophy, described by Hatfield and Lefley (63, 64), espouses that mental illness is biologically grounded; in particular, it eschews a family-based view of etiology. The ideology of biologically based illness provides the members of the National Alliance who are parents of psychiatrically disabled patients with relief from the distress associated with guilt over their children's illnesses. In addition, like the belief systems of the charismatic religious groups and other zealous

self-help programs, it also serves to organize the behavior of members.

The parent group movement, with origins in Atlanta in 1976, is another example of how the charismatic group phenomenon can serve as a vehicle for zealous self-help by families dealing with psychiatric illness. It was mobilized to address a perceived epidemic of substance abuse among middle-class youngsters and is credited by the federal government with establishing more than 1,000 local groups that played an important part in the recent decrease in marijuana use by adolescents (65). It dramatically illustrates the emergence of self-help movements in the face of a perceived lack of professional help; charismatic groups typically arise in the face of despair with established authorities. Furthermore, there are certain important similarities between the parent group members my associates and I studied and the members of religiously oriented charismatic groups (66). For example, there was no significant difference in scores on cohesiveness with fellow members when parent group respondents and Unification Church members were compared. Parent group members' responses showed intense ideological commitment, especially with regard to the dangers of marijuana use. This cohesiveness and mutual commitment allowed the program to effect major behavior changes in the child-rearing practices of its members as well as incursions into the political arena.

This grass-roots movement also spawned peer-based adolescent drug treatment programs, often in geographical areas where there was little professional assistance available for substance-abusing teenagers. Although many youngsters were helped, the following experience illustrates the need for psychiatric consultation to peer-led groups in order to assure proper diagnosis and treatment. In some ways it parallels case 2, where symptoms were precipitated by alienation from a zealous cohesive group.

*Case 7.* A 17-year-old was admitted because of daily marijuana smoking to a community residence affiliated with the parent group movement. After several weeks of intensive milieu treatment that relied heavily on recovering adolescent peers, he was judged "unwilling" to give up his commitment to the "drug life" and was asked to leave. He responded to this as a profound rejection, intensified by the close-knit nature of the group, and became severely depressed. Shortly thereafter he made a suicide attempt, necessitating his hospitalization in a general psychiatric facility. Subsequent interviews revealed that he had also been severely depressed on admission to the community residence. He was later successfully treated with supportive therapy and imipramine. His diagnoses were major depression, recurrent, unspecified (296.30), and cannabis abuse (305.20).

### CONCLUSIONS

The model of the charismatic group is applicable to many zealous self-help groups that both relieve and generate psychiatric illness. Because of this, it is im-



portant for psychiatrists to consider what roles they may assume in relation to these movements.

Consultation to symptomatic members can be important. Zealous self-help groups generally apply a specific paradigm to the management of all those who join. Proper diagnosis and treatment are therefore essential for psychiatric problems that are not effectively addressed in the group milieu. Consultation to the group itself may raise further issues, since charismatic groups usually expect some measure of subordination to their ideology from professionals whom they engage. For example, the new religious movements are very protective of the theological implications of any psychiatric interventions. Avoiding issues that reflect on the formal beliefs of the group can be essential to maintaining a viable professional stance; this, however, may raise problems in providing proper care.

Another role for psychiatrists lies in the development of zealous group programs designed to meet the clinical needs in an institutional treatment setting. Many patients treated by professionals, such as the chronically mentally ill and those receiving methadone maintenance therapy, maintain a relatively passive stance in relation to the goals for rehabilitation set by their institutional caregivers. Furthermore, the value of the peer-based models in the addiction community suggests their applicability in settings where patients with both addictive and general psychiatric diagnoses are treated. Without the zealous support such groups can generate for an ideology of abstinence, continued drug use may continue to plague the supposedly treated dual-diagnoses patient.

Psychiatrists are also in an excellent position to investigate how self-help groups operate. For example, we have seen that acute distress is a motivator to join, as illustrated by Recovery and AA. How such distress works to motivate engagement and which symptoms are most influential remain to be understood.

Another research issue to be investigated is the duration of membership. As reported by Omark (67), people who join programs like Recovery may remain committed for many years and are often highly dependent. The same is seen among longstanding members of 12-step programs. On the other hand, protracted membership may be necessary in many cases to ensure remission. Research into the proper length of engagement to address initial symptoms has yet to be done.

With regard to the ideological underpinnings of such groups, it is important to learn what systemic needs lead some groups to become involved in faddish and ill-advised therapeutic ideologies such as megavitamin therapy, as did the now disbanded group Schizophrenics Anonymous (68), or to engage in bizarre and criminal behavior, such as Synanon, a drug treatment program (69).

Ultimately, zealous group modalities may come to serve as useful adjuncts to psychiatric care. Experience shows, however, that the leadership in such groups should not rest solely in the hands of a few leaders and that members should have access to objective scientific

observations on the problems they address, thereby avoiding cultic seclusiveness. They should define clear limits on the degree to which they impinge on the various areas of function of members' lives, and they should also maintain an open and cooperative relationship with appropriate professionals in the community. If groups of this nature can be promoted and studied for their effectiveness as collaborators in the treatment process, resources available to the mental health field may be materially enhanced.

## REFERENCES

1. Needleman J, Baker G (eds): *Understanding New Religions*. New York, Seabury Press, 1978
2. Galanter M (ed): *Cults and New Religious Movements: A Report of the American Psychiatric Association*. Washington, DC, APA, 1989
3. Galanter M: The "relief effect": a sociobiological model for neurotic distress and large-group therapy. *Am J Psychiatry* 1978; 135:588-591
4. Galanter M: *Cults: Faith, Healing, and Coercion*. New York, Oxford University Press, 1989
5. Nelson GK: The membership of a cult: the Spiritualists National Union. *Review of Religious Research* 1972; 170:13
6. Katz AH, Bender EI (eds): *Self Help Groups in the Modern World*. New York, New Viewpoints, 1976
7. Kephart WM: *Extraordinary Groups: The Sociology of Unconventional Life-Styles*. New York, St Marten's Press, 1976
8. Cartright D, Zander A (eds): *Group Dynamics: Research and Theory*. Evanston, Ill, Row, Peterson, 1962
9. Pattison M: A theoretical-empirical base for social systems therapy, in *Current Perspectives in Cultural Psychiatry*, 1st ed. Edited by Foulks EF, Favazza A. New York, Halsted Press, 1977
10. Kilbourne B, Richardson JT: Psychotherapy and new religions in a pluralistic society. *Am Psychol* 1984; 39:237-251
11. Levine S: Alienated Jewish youth and religious seminars, in *Psychodynamic Perspectives on Religion, Sect and Cult*. Edited by Halperin DA. Boston, John Wright-PSG, 1983
12. Galanter M, Buckley P: Evangelical religion and meditation: psychotherapeutic effects. *J Nerv Ment Dis* 1978; 166:685-691
13. Kennedy JG: Nubian Zar ceremonies and psychotherapy. *Human Organization* 1967; 4:185-192
14. Singer M, Borrero MG: Indigenous treatment for alcoholism: the case of Puerto Rican spiritualism. *Medical Anthropology: Cross-Cultural Studies in Health and Illness* 1984; 8:246-273
15. Galanter M, Rabkin R, Rabkin J, et al: The "Moonies": a psychological study of conversion and membership in a contemporary religious sect. *Am J Psychiatry* 1979; 136:165-170
16. Kleinman A, Gale JG: Patients treated by physicians and folk healers: a comparative outcome study in Taiwan. *Cult Med Psychiatry* 1982; 6:405-423
17. Proudfoot W, Shaver P: Attribution theory and the psychology of religion. *J for the Scientific Study of Religion* 1976; 14:317-330
18. Favazza AR, Faheem AD: Indigenous healing groups, in *Comprehensive Group Psychotherapy*. Edited by Kaplan HI, Sadock BJ. Baltimore, Williams & Wilkins, 1983
19. Leighton A, Leighton D: Elements of psychotherapy in Navajo religion. *Psychiatry* 1941; 4:515-523
20. Kaplan B, Johnson D: The social meaning of Navajo psychopathology, in *Magic, Faith, and Healing*. Edited by Kiev A. New York, Free Press, 1964
21. Lifton RJ: *Thought Reform and the Psychology of Totalism*. New York, WW Norton, 1961
22. Wenegeat B: Religious cult membership: a sociobiologic model, in *Cults and New Religious Movements: A Report of the American Psychiatric Association*. Edited by Galanter M. Washington, DC, APA, 1989
23. Ferster CB: *Control of Behavior in Chimpanzees and Pigeons* by

- Time Out From Positive Reinforcement. Psychol Monogr 1958; 461
24. Rodin MB: Getting on the program: a biocultural analysis of Alcoholics Anonymous, in *The American Experience With Alcohol: Contrasting Cultural Perspectives*. Edited by Bennett L, Ames GM. New York, Plenum, 1985
  25. Galanter M: Psychological induction into the large-group: findings from a modern religious sect. *Am J Psychiatry* 1980; 137: 1574-1579
  26. Galanter M: Engaged members of the Unification Church. *Arch Gen Psychiatry* 1983; 40:1197-1202
  27. Galanter M: "Moonies" get married: a psychiatric follow-up study of a charismatic religious sect. *Am J Psychiatry* 1986; 143:1245-1249
  28. Galanter M: Unification Church ("Moonie") dropouts: psychological readjustment after leaving a charismatic religious group. *Am J Psychiatry* 1983; 140:984-989
  29. Clark JG Jr: Cults. *JAMA* 1979; 242:279-281
  30. Singer M: Therapy with ex-cult members. *J National Assoc of Private Psychiatric Hosp* 1978; 9(4):14-18
  31. Brown PL: Troubled millions heed call of self-help groups. *New York Times*, July 16, 1988, p A1
  32. Frank J: *Persuasion and Healing*. New York, Schocken Books, 1973
  33. Caplan G: *Support Systems and Community Mental Health: Lectures on Concept Development*. New York, Behavioral Publications, 1974
  34. Speck RV, Attneave CL: *Family Networks*. New York, Pantheon, 1973
  35. Schoenfeld P, Halevy J, Hemley-van der Velden E, et al: The long-term outcome of network therapy. *Hosp Community Psychiatry* 1986; 37:373-376
  36. Lieberman MA, Solow N, Bond GR: The psychotherapeutic impact of women's consciousness-raising groups. *Arch Gen Psychiatry* 1979; 36:161-168
  37. Simon J: Observations on 67 patients who took Erhard Seminars Training. *Am J Psychiatry* 1978; 135:686-691
  38. Glass LL, Kirsch MA, Parris FN: Psychiatric disturbances associated with Erhard Seminars Training, I: a report of cases. *Am J Psychiatry* 1977; 134:245-247
  39. Kirsch MA, Glass LL: Psychiatric disturbances associated with Erhard Seminars Training, II: additional cases and theoretical considerations. *Am J Psychiatry* 1977; 134:1254-1258
  40. Wechsler H: The self-help organization in the mental health field: Recovery, Inc, a case study. *J Nerv Ment Dis* 1960; 130: 297-314
  41. Galanter M: Zealous self-help groups as adjuncts to psychiatric treatment: a study of Recovery, Inc. *Am J Psychiatry* 1988; 145:1248-1253
  42. Toseland RW, Hacker L: Self-help groups and professional involvement. *Social Work* 1982; 27:341-347
  43. Lee DT: Recovery, Inc: aid in the transition from hospital to community. *Ment Hygiene* 1971; 55:194-198
  44. Rappaport J, Seidman E, Toro PA, et al: Collaborative research with a mutual help organization. *Social Policy*, winter 1985, pp 12-24
  45. General Service Office of Alcoholics Anonymous: *World AA Directory* 1987. New York, AA World Services, 1987, p iii
  46. Rudy DR: *Becoming Alcoholic: Alcoholics Anonymous and the Reality of Alcoholism*. Carbondale, Southern Illinois University Press, 1986
  47. Thomsen R: Bill W. New York, Harper & Row, 1985, pp 220-221
  48. Trice HM, Roman PM: Sociopsychological predictors of affiliation with Alcoholics Anonymous: a longitudinal study of "treatment success." *Soc Psychiatry* 1970; 5:51-59
  49. Eckhardt W: Alcoholic values and Alcoholics Anonymous. *Q J Stud Alcohol* 1967; 28:277-288
  50. Trice HM, Beyer JM: The routinization of charisma in two movement organizations, in *Research in Organizational Behavior*, vol 8. Edited by Staw BM, Cummings LL. Greenwich, Conn, JAI Press, 1986
  51. Jilek WG: *Salish Indian Mental Health and Cultural Change*. Toronto, Holt, Rinehart and Winston, 1974
  52. Talbott GD, Martin CA: Treating impaired physicians: 14 keys to success. *Va Med* 1986; 113:95-99
  53. Galanter M, Talbott D, Gallegos K, et al: Combined Alcoholics Anonymous and professional care for addicted physicians. *Am J Psychiatry* 1990; 147:64-68
  54. DeLeon GD: The therapeutic community: status in evolution and evolution. *Int J Addict* 1985; 20:823-844
  55. DeLeon GD: Therapeutic community research: overview and implication, in *Therapeutic Communities for Addictions*. Edited by DeLeon GD, Zeigenfuss JT. Springfield, Ill, Charles C Thomas, 1986
  56. Mosher LR, Menn A, Matthews SM: Soteria: evaluation of a home-based treatment for schizophrenia. *Am J Orthopsychiatry* 1975; 45:455-467
  57. Laing RD: *The Divided Self*. London, Tavistock Publications, 1960
  58. Mosher LR, Menn AZ: Community residential treatment for schizophrenia: a two-year follow-up. *Hosp Community Psychiatry* 1978; 29:715-723
  59. Galanter M, Castaneda R, Salamon I: Institutional self-help for alcoholism: clinical outcome. *Alcoholism (NY)* 1987; 11:424-429
  60. Hudolin V: Klubovi Liječenih Alkoholikara (Clubs of Treated Alcoholics). Zagreb, Juma, 1982
  61. Galanter M: Alcoholism in the USSR and Yugoslavia: effects of the social context on treatment. *Currents in Alcoholism* 1981; 8:183-194
  62. Vine P, Beels CC: Support and advocacy groups for the mentally ill, in *Psychosocial Treatment in Schizophrenia*. Edited by Herz MI, Keith S, Docherty J. Amsterdam, Elsevier (in press)
  63. Hatfield AB, Lefley HP: Preface, in *Families of the Mentally Ill: Coping and Adaptation*. New York, Guilford Press, 1987
  64. Lefley HP: Families of the mentally ill in cross-cultural perspectives. *Psychosoc Rehab J* 1985; 8(4):57-75
  65. National Institute on Drug Abuse: *Prevention at the grass roots*. Prevention Resources 1982; 6:1-4
  66. Galanter M, Gleaton T, Marcus CE, et al: Self-help groups for parents of young drug and alcohol abusers. *Am J Psychiatry* 1984; 141:889-891
  67. Omark RC: The dilemma of membership in Recovery, Inc, a self-help ex-mental patients' organization. *Psychol Rep* 1979; 44(3, part 2):1119-1125
  68. Ryback RS: Schizophrenics Anonymous: a treatment adjunct. *Psychiatry Med* 1971; 2:247-253
  69. Yablonsky L: *Synanon: The Tunnel Back*. New York, Macmillan, 1970

# Affective Spectrum Disorder: Does Antidepressant Response Identify a Family of Disorders With a Common Pathophysiology?

James I. Hudson, M.D., and Harrison G. Pope, Jr., M.D.

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*Response to pharmacologic treatments may identify groups of disorders with a common pathophysiology. The authors applied a treatment-response model, based on four classes of antidepressants (tricyclic types, monoamine oxidase inhibitors, serotonin uptake inhibitors, and atypical agents), to the medical literature. The model identified eight disorders that may share a pathophysiologic abnormality: major depression, bulimia, panic disorder, obsessive-compulsive disorder, attention deficit disorder with hyperactivity, cataplexy, migraine, and irritable bowel syndrome. Phenomenologic and family studies support this grouping. If the model is validated, this family of disorders, which the authors term "affective spectrum disorder," would represent one of the most prevalent diseases in the population.*

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Many psychiatric and medical disorders respond to antidepressant medications. Because these disorders may respond fully to antidepressants from several unrelated chemical classes, it follows that they may share a pathophysiologic "step" in the etiologic chain of steps required for their expression. We describe the development and application of a model designed to identify members of this proposed family of disorders, here termed "affective spectrum disorder." The disorders identified include major depression, bulimia, panic disorder, obsessive-compulsive disorder, attention deficit disorder with hyperactivity, cataplexy,

migraine, and irritable bowel syndrome. Several other disorders, such as posttraumatic stress disorder and atypical facial pain, nearly meet the criteria of the model as well.

Even before the antidepressant era, some theorists suspected a relationship among several of these disorders on the basis of clinical phenomenologic observations alone. Modern phenomenologic and family studies have continued to demonstrate comorbidity between the various forms of affective spectrum disorder. Thus, there is cross-validation between these findings and those of the model, reinforcing the hypothesis that affective spectrum disorder represents a valid entity.

The model generates a series of testable predictions that are presented at the end of this paper.

## RATIONALE FOR A TREATMENT-RESPONSE MODEL

Throughout the history of medicine, response to treatment has been used as one method to identify disorders that share a pathophysiologic abnormality. Such an approach might be illustrated by the findings of eighteenth-century physicians who treated "sea diseases" in the British navy (1, 2). Seamen on long ocean voyages developed many disorders, among them putrid gums, lassitude, spots, and weak knees. These four disorders all responded to certain food groups, including citrus fruits, fresh vegetables, and raw meats. Other common sea diseases, however, such as fevers, consumptions, and rheumatisms, showed little response to any dietary treatment. These observations supported the hypothesis that putrid gums, lassitude, spots, and weak knees—but not fevers, consumptions, or rheumatisms—might be due to a common underlying abnormality. This hypothesis proved correct: the various features of scurvy are attributable to ascorbic acid deficiency and respond to foods containing this vitamin.

In general, then, if one observes disorders  $D_1, D_2, \dots, D_N$ , all of which respond to treatment classes  $C_1, C_2, \dots, C_N$  (which in modern medicine usually represent drug classes rather than foods), a likely hypoth-

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Received April 21, 1989; revision received July 28, 1989; accepted Aug. 10, 1989. From the Biological Psychiatry Laboratory, Laboratories for Psychiatric Research, and Psychosis Program, McLean Hospital; and the Department of Psychiatry, Harvard Medical School, Boston. Address reprint requests to Dr. Hudson, McLean Hospital, 115 Mill St., Belmont, MA 02178.

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esis is that  $D_1, D_2, \dots, D_N$  share a specific physiologic abnormality, which drug classes  $C_1, C_2, \dots, C_N$ , although differing in chemical structure and in many of their other clinical pharmacologic effects, ameliorate through a common action.

Note that it may not be sufficient for this argument to demonstrate that  $D_1, D_2, \dots, D_N$  respond to a single drug class  $C_1$ . For example, major depression, a psychiatric disorder, and kala azar (cutaneous leishmaniasis), a protozoal infection, both respond to clomipramine. But these diseases are unrelated—as evidenced by the observation that other drug classes effective for depression, such as monoamine oxidase inhibitors (MAOIs) and serotonin uptake inhibitors, are ineffective for kala azar. The case is different, however, if disorders  $D_1, D_2, \dots, D_N$  are all found to respond to drugs from the same series of different chemical classes. It then becomes improbable that drug families  $C_1$  through  $C_N$  all treat  $D_1$  by one mechanism of action, while treating  $D_2$  by a second, entirely unrelated mechanism which, by chance, they also share, and so forth through  $D_N$ . A more parsimonious explanation is that there is only one mechanism of action common to all of the several drug classes and that these classes ameliorate  $D_1, D_2, \dots, D_N$  through this mechanism, acting on a specific physiologic abnormality that  $D_1, D_2, \dots, D_N$  share.

A promising application for this model in contemporary medicine is with so-called antidepressants. These drugs fall into distinct chemical classes, and many psychiatric and medical disorders respond to agents from several of these classes. Thus, a family of disorders, linked by a possible common physiologic abnormality, may be identified. This family is here provisionally termed “affective spectrum disorder.” Although this term has been used in the past, with various definitions (3), it will be defined in this paper by specific antidepressant-response criteria and not by any previous set of criteria. It should also be noted that the choice of the word “affective” is arbitrary, reflecting simply the historical fact that antidepressants were generally first used to treat depression and only later found to be effective in other disorders.

## DESIGN OF THE MODEL

We reviewed the current classifications of antidepressants (4–6) and derived the following drug classes: tricyclic type (tricyclic antidepressants, such as imipramine, and chemically similar agents, such as maprotiline and viloxazine), MAOIs (potent inhibitors of MAO, such as phenelzine and tranylcypromine), serotonin uptake inhibitors (potent and selective inhibitors of serotonin uptake, such as fluoxetine, fluvoxamine, and zimelidine), and atypical agents (drugs such as bupropion, mianserin, nomifensine, and trazodone, with profiles of action different from those of other drug classes). We did not include in our analysis drugs classified primarily as antimanic agents, anxiolytics, anti-

convulsants, or stimulants. Although drugs such as lithium, alprazolam, carbamazepine, and amphetamine are probably effective in major depression (4, 7–9), they have been studied less extensively than standard antidepressants in major depression and much less extensively in many other disorders, making them less useful for our model. Similarly, a nonpharmacologic treatment, ECT, although clearly effective in major depression (4, 6), has been insufficiently studied in most other disorders.

We then surveyed the literature for treatment studies that used these classes of antidepressants in all psychiatric and medical disorders listed in ICD-9-CM (10). We evaluated disorders that consistently respond to antidepressants from two or more classes as candidate members of the affective spectrum disorder family. We omitted from evaluation disorders such as other affective disorders, schizoaffective disorder, and organic affective syndrome, since these conditions are already defined primarily by the presence of affective symptoms. We also omitted a few poorly defined disorders, including tension headache and back pain, because of the highly variable diagnostic criteria used in antidepressant studies of these entities.

We rated response to a given antidepressant on a 5-point scale, from (–) to (++++), (see table 1 [footnote a] for definitions of ratings). When response to a particular drug class had not been assessed, we assigned a rating of insufficient data. We considered a single case report or chart review study as insufficient data.

We classified disorders at two levels of confidence on the basis of antidepressant response. A level of potentially high specificity but possibly low sensitivity, designated as probable affective spectrum disorder, required that the disorder respond to drugs from at least three of the four antidepressant classes in placebo-controlled studies (rating of +++ or ++++ in each class). A second level, of higher sensitivity but possibly lower specificity, designated possible affective spectrum disorder, required that the disorder respond to drugs from at least three of the four classes (rating of ++ or better), with efficacy in placebo-controlled studies (rating of +++ or ++++) established in at least one.

## FINDINGS

The following four disorders, in addition to major depression, met criteria for probable affective spectrum disorder: bulimia, panic disorder, obsessive-compulsive disorder, and attention deficit disorder with hyperactivity (table 1). The following three additional disorders attained a rating of possible affective spectrum disorder: cataplexy (the syndrome of “drop attacks,” characteristically observed in narcolepsy), migraine, and irritable bowel syndrome (table 2).

Several other candidate disorders did not reach criteria for probable or possible affective spectrum disorder.

TABLE 1. Response of Probable Forms of Affective Spectrum Disorder to Antidepressants

Disorder	Tricyclic Type			MAOIs			Serotonin Uptake Inhibitors		
	Medication	Rating <sup>a</sup>	Studies	Medication	Rating <sup>a</sup>	Studies	Medication	Rating <sup>a</sup>	Studies
Bulimia	Desipramine	++++	11-13	Phenelzine	++++	14, 15	Fluoxetine	++++	16, 17
	Imipramine	++++	20-23	Isocarboxazid	+++	24, 25			
	Amitriptyline	+	29 <sup>b</sup>	Tranylcypromine	++	31-35			
Panic disorder <sup>c</sup>	Clomipramine	++++	40, 41	Phenelzine	++++	42, 43	Zimelidine	+++	44
	Imipramine	++++	42-44, 47-54 <sup>d</sup>				Fluoxetine	++	56, 57
	Desipramine	++	59-61				Fluvoxamine	++	62-65
	Nortriptyline	++	59, 66						
	Maprotiline	+	62, 67, 68						
Obsessive-compulsive disorder	Clomipramine	++++	69-77 <sup>e</sup>	Phenelzine	++	79-82	Fluvoxamine	++++	83, 84
	Doxepin	++	86, 87	Tranylcypromine	++	82, 88, 89	Fluoxetine	++	90-95
	Amitriptyline	+	102-104	Clorgyline	-	74	Zimelidine	+	105-108
	Imipramine	+	87, 102, 105, 109-114 <sup>e</sup>						
	Desipramine	-	106, 115-117						
Attention deficit disorder with hyperactivity <sup>f</sup>	Nortriptyline	-	73						
	Desipramine	++++	119-121	Clorgyline	+++	122			
	Clomipramine	+++	119	Tranylcypromine	+++	122			
	Imipramine	++	127	L-Deprenyl	-	128			

<sup>a</sup>Uncontrolled studies not cited if two or more placebo-controlled studies showed efficacy of drug. Ratings: ++++=supported by two or more placebo-controlled studies, with little or no counterevidence; +++=supported by one placebo-controlled study and, usually, open studies, with little or no counterevidence; ++=supported by at least one open study, with possibly some counterevidence; +=supported by balance of evidence, but evidence of efficacy limited or significant counterevidence present; -=not supported by balance of evidence, but limited evidence for efficacy may be present; —=insufficient data.

<sup>b</sup>Inadequate drug doses may have contributed to lack of efficacy observed (see Pope and Hudson [30]).

<sup>c</sup>Includes panic disorder with or without agoraphobia; most studies involved patients with phobic avoidance.

<sup>d</sup>Most, but not all, studies showed superiority of drug to placebo (see Lydiard and Ballenger [55]).

<sup>e</sup>For further analysis of these studies, see White and Cole (78).

<sup>f</sup>Studies using pre-DSM-III criteria are not easily compared and hence are not included (see Aschenbach [118]).

TABLE 2. Response of Possible Forms of Affective Spectrum Disorder to Antidepressants

Disorder	Tricyclic Type			MAOIs			Serotonin Uptake Inhibitors		
	Medication	Rating <sup>a</sup>	Studies	Medication	Rating <sup>a</sup>	Studies	Medication	Rating <sup>a</sup>	Studies
Cataplexy	Viloxazine	+++	129	L-Deprenyl	++	130 <sup>b</sup>	Femoxetine	+++	132
	Clomipramine	++	133-139	Phenelzine	++	140	Fluoxetine	++	139
	Desipramine	++	137, 141				Fluvoxamine	++	138
	Imipramine	++	135, 137, 141-143				Zimelidine	++	144
	Protriptyline	++	145, 146						
Migraine	Amitriptyline	++++	147-149	Phenelzine	++	150, 151			
	Clomipramine	+	154, 155	Tranylcypromine	++	151			
Irritable bowel syndrome	Desipramine	++++	156, 157	Phenelzine	++	158, 159			
	Trimipramine	++++	161-163						
	Amitriptyline	+++	164-166						
	Doxepin	++	160, 163, 167, 168						
	Nortriptyline	++	169						

<sup>a</sup>See table 1 for definitions of ratings of efficacy.

<sup>b</sup>Earlier study by the same group (131), using lower doses, failed to show efficacy.

der (table 3). Some of these disorders fell below criteria simply because sufficient trials, especially with non-tricyclic types of agents, had not been reported. Thus, these candidates should not be considered as rejected, but rather as disorders for which insufficient data exist. Particularly promising candidates for forms of affective spectrum disorder are posttraumatic stress disorder and atypical facial pain.

We then reviewed phenomenologic studies that examined the lifetime prevalence of other disorders in

patients with an index diagnosis of a given form of affective spectrum disorder and family studies that assessed the prevalence of various disorders in the relatives of such individuals. Most studies have tested the relationship between the proposed forms of affective spectrum disorder and major affective disorder. Phenomenologic studies consistently have shown high rates of major affective disorder in patients with all of the proposed forms of affective spectrum disorder except cataplexy, which has been investigated less exten-

TABLE 1. (continued)

Atypical Agents		
Medication	Rating <sup>a</sup>	Studies
Bupropion	+++	18, 19
Nomifensine	+++	14, 26–28
Trazodone	+++	31, 36–38
Mianserin	—	39 <sup>b</sup>
Trazodone	+	45, 46
Bupropion	—	58
Mianserin	+++	70, 85
Trazodone	++	96–101
Bupropion	++++	123, 124
Mianserin	—	125, 126

TABLE 2. (continued)

Atypical Agents		
Medication	Rating <sup>a</sup>	Studies
—		
Mianserin	++++	152, 153
Trazodone	++	160

sively (table 4). Conversely, patients with major affective disorder have been reported to show high rates of panic disorder (220, 233, 238, 275), obsessive-compulsive disorder (220, 276), attention deficit disorder with hyperactivity (277), and migraine (278, 279). Community studies and other studies of nonpatient samples have also found frequent comorbidity of major affective disorder with bulimia (220), panic disorder (280, 281), obsessive-compulsive disorder (280,

282), attention deficit disorder with hyperactivity (283), and migraine (279, 281, 284).

Family studies consistently have shown high rates of major affective disorder in the relatives of patients with bulimia, panic disorder, and attention deficit disorder with hyperactivity; family data for other forms of affective spectrum disorder are more limited (table 4). Conversely, patients with major affective disorder have been reported to show high familial rates of panic disorder (285), attention deficit disorder with hyperactivity (286–290), and migraine (279).

Some studies have further tested the model by exploring the relationship between other disorders within the family of affective spectrum disorder. For example, high rates of panic disorder have been found in a majority of studies of patients with bulimia (209, 216, 220), obsessive-compulsive disorder (246, 247, 291), migraine (151), and irritable bowel syndrome (269, 274); high rates of obsessive-compulsive disorder have been found in a majority of studies of patients with bulimia (209, 220, 221) and panic disorder (292–294); and high rates of migraine (295) and irritable bowel syndrome (159) have been found in patients with panic disorder.

## DISCUSSION

The treatment-response model developed in this paper identified the following seven probable or possible forms of affective spectrum disorder in addition to major depression itself: bulimia, panic disorder, obsessive-compulsive disorder, attention deficit disorder with hyperactivity, cataplexy, migraine, and irritable bowel syndrome. Several other disorders, such as post-traumatic stress disorder and atypical facial pain, fell only slightly below the criteria of the model. The identified forms of affective spectrum disorder, including major depression, afflict a large portion of the population (136, 280, 283, 296–298).

Several earlier theorists, writing long before the advent of antidepressant medications, suspected an association between many of these disorders on the basis of clinical observations alone. In 1934, Lewis (299) noted high rates of panic disorder and obsessive-compulsive disorder in melancholic patients and advocated a unitary view of affective and anxiety disorders. Even earlier, Janet (300) argued for the clinical unity of the *agitations forcées*—a family of disorders that encompassed obsessive-compulsive disorder; phobic disorders; panic disorder; bulimia (301); pain syndromes, including cases suggestive of migraine and atypical facial pain; and, among other physiologic disorders, gastrointestinal conditions suggestive of irritable bowel syndrome. Janet found the *agitations forcées* frequently associated with dysthymia and major depression (*psychasthénie* and *neurasthénie*, respectively) but distinct from hysteria. Modern phenomenologic and family studies, as noted earlier, support the impres-



**TABLE 3. Disorders for Which at Least Two Classes of Antidepressants Have Been Tested But Which Do Not Meet Criteria for Forms of Affective Spectrum Disorder**

Disorder	Evidence for Antidepressant Response <sup>a</sup>
Anorexia nervosa	Results of controlled studies of amitriptyline were negative (170) or equivocal (171); results of open studies of MAOIs (172, 173) and trazodone (172) were equivocal
Posttraumatic stress disorder	Results of controlled studies of amitriptyline (174) and imipramine (175) were positive, but results of a controlled study of desipramine were negative (176) <sup>b</sup> ; results of one controlled study (175) and numerous open studies (177–184) of phenelzine were positive, but results of one controlled study (185) of phenelzine were negative
Social phobia	Results of a controlled study of phenelzine (186) were positive; results of an uncontrolled study of imipramine (187) were positive
Generalized anxiety disorder	One positive (188) and one negative (189) controlled study of imipramine; results of a controlled study of trazodone (189) were negative
Tourette's syndrome	Tricyclics reported to improve (190–192), exacerbate (193–195), or not affect (195–198) symptoms; one uncontrolled study of fluoxetine (199) had equivocal results
Atypical facial pain	Results of controlled studies of dothiepin (200) and phenelzine (201) were positive
Obstructive sleep apnea <sup>c</sup>	Two positive (202, 203) and one negative (204) controlled study of protriptyline; results of an open study of nomifensine were equivocal (205)

<sup>a</sup>“Controlled” indicates placebo controlled; open studies cited only when controlled studies of a given drug class are conflicting or not available; single case reports are not cited.

<sup>b</sup>Drug levels obtained were generally lower than those effective in major depression.

<sup>c</sup>Not a disorder in ICD-9-CM but evaluated because of existing literature on antidepressant response.

**TABLE 4. Evidence From Phenomenologic and Family Studies of High Rates of Major Affective Disorder in Patients With Other Forms of Affective Spectrum Disorder**

Disorder	Phenomenologic Studies <sup>a</sup>		Family Studies	
	Rating <sup>b</sup>	Studies	Rating <sup>b</sup>	Studies
Bulimia <sup>c</sup>	++++	206–225	++++	206, 207, 210, 213 <sup>d</sup> –215, 217, 223–227 <sup>d</sup> , 228
Panic disorder	++++	229–240	+++	229, 241, 242 <sup>c</sup> , 244
Obsessive-compulsive disorder	++++	245–248	+	249–252
Attention deficit disorder with hyperactivity <sup>f</sup>	+++	253–255	+++	254, 256–258 <sup>d</sup>
Cataplexy	++	259–265	—	259, 260
Migraine	++++	151, 266–268	—	
Irritable bowel syndrome	++++	269–274	—	

<sup>a</sup>Phenomenologic studies lacking operational diagnostic criteria not cited if two or more such studies using operational criteria were available.

<sup>b</sup>Ratings: ++++ = supported by two or more studies using structured interviews to diagnose patients (phenomenology studies) or relatives (family studies) by operational criteria, with family studies controlled and little or no counterevidence; +++ = supported by two or more studies using operational criteria to diagnose patients (phenomenology) or relatives (family), with family studies controlled and possibly some counterevidence; ++ = supported by studies using nonoperational diagnostic criteria (phenomenology) or uncontrolled studies (family), with possibly some counterevidence; + = supported by the balance of evidence, but either evidence limited or significant counterevidence present; — = insufficient data: available studies, if any, limited and cannot be interpreted as supporting or refuting a relationship to major affective disorder.

<sup>c</sup>Patients in some studies displayed both anorexia nervosa and bulimia.

<sup>d</sup>Study found high rates of major affective disorder in relatives of control probands as well as in relatives of index probands.

<sup>e</sup>Although study found low rates of “primary depression,” it found high rates of “secondary depression” in relatives of probands with panic disorder (see reanalysis of this study by Weissman [243]).

<sup>f</sup>Studies using pre-DSM-III criteria are not easily compared and hence are not included (see Aschenbach [118]).

sions of writers such as Lewis and Janet and cross-validate the findings of the treatment-response model.

Possible criticisms of the model, however, should be considered. First, not all antidepressant studies in tables 1 and 2 had positive findings, nor do all symptoms of all patients respond in any given study. To some extent, of course, such imperfection is to be expected: even in major depression itself, the reported efficacy of different antidepressants varies widely among studies, and studies of even the best-established agents have sometimes reported negative findings (302). But this fact alone does not fully explain the variability of an-

tidepressant response observed in different forms of affective spectrum disorder. Some disorders, such as cataplexy and migraine, respond quickly to low doses of these medications, and others, such as obsessive-compulsive disorder, respond slowly and incompletely even to high doses. Such variation might suggest that these disorders are unrelated and that independent “fast” and “slow” drug mechanisms are operating on independent pathophysiologic abnormalities. This possibility is illustrated by the earlier example of clomipramine, which has a rapid “leishmanicidal” effect and an independent, slow antidepressant effect. The

various forms of affective spectrum disorder, however, respond not to one but to three or more chemically different classes of antidepressants. To assume that all of these classes display a mutual fast mechanism of action at one site and a separate mutual slow mechanism at a different site seems improbable. A more parsimonious hypothesis is that the different forms of affective spectrum disorder share a single physiologic abnormality and that variations in the etiology, severity, and expression of that abnormality determine the efficiency of drug response.

On the other hand, one cannot exclude the possibility that a proposed form of affective spectrum disorder might have two independent etiologies. For example, there might be two types of migraine: an affective spectrum disorder type that responds to antidepressants and a non-affective spectrum disorder type that does not. In most of the proposed forms of affective spectrum disorder, however, the percentage of patients showing some response to antidepressants is a substantial majority. This observation argues that non-affective spectrum disorder types of these disorders, if present, account for a minority of cases.

The case for non-affective spectrum disorder types of the disorders might seem buttressed by the observation that many of the disorders respond to other pharmacologic and nonpharmacologic treatments that are relatively ineffective for major depression: panic disorder may respond to beta-adrenergic blockers (303), migraine to ergot alkaloids (304), and irritable bowel syndrome to dietary manipulation (305). Such observations, however, are irrelevant to the present argument: while proposing that antidepressants treat the various forms of affective spectrum disorder at a common physiologic "point," the model allows that nonantidepressant agents might treat them at other "points."

Also irrelevant are hypotheses regarding the etiologic chain of steps that lead to the expression of the various disorders or the therapeutic chain of steps by which antidepressants treat them. To apply the model, one need not consider whether, say, bulimia is "secondary" to major depression or vice versa, nor whether antidepressants act by means of neurotransmitters or at some other physiologic level. The model assumes that the organism is a black box and therefore argues only that, for each form of affective spectrum disorder, *one* step in the etiologic chain is the same: a necessary (but probably not sufficient) physiologic abnormality upon which antidepressants act to treat that disorder. By analogy, within the family of autoimmune disease, the various disorders (such as systemic lupus erythematosus, rheumatoid arthritis, and type I diabetes mellitus) have widely differing etiologic chains of steps. But these chains all share one necessary step: an immunologic reaction to host antigens.

Of course, one must allow that in the case of affective spectrum disorder, the mutual step might be a trivial one, with the disorders linked by an abnormality of little clinical or theoretical interest. For example,

pain is a feature of many medical disorders, and pain responds to several different classes of analgesics. However, it would be of little heuristic value to class all such conditions as "pain spectrum disorder" because analgesics usually treat only the isolated symptom of pain and not the disorder itself. By contrast, antidepressants, when fully effective, appear to treat the full clinical syndrome in each form of affective spectrum disorder (11, 35, 47, 70, 82, 122, 132, 137, 150, 160, 163, 306–308). Thus, the hypothesized common abnormality in affective spectrum disorder is probably not trivial.

Finally, it must be acknowledged that the model offers only a first approximation in the classification of the forms of affective spectrum disorder: finer differentiations among the various disorders may become evident with pharmacologic dissection (309). For example, obsessive-compulsive disorder appears to respond better to clomipramine than to desipramine, possibly because clomipramine is a serotonin agonist and desipramine is not (116). Similarly, it has been proposed that disorders associated with atypical depressive symptoms (310), such as bulimia (34), respond better to MAOIs than to other classes of antidepressants, implying possible differences in mechanisms. And some antidepressants may be entirely ineffective for some forms of affective spectrum disorder, as illustrated possibly by the negative findings of the one available open trial of bupropion in panic disorder (58). To resolve such questions will require a more complete inventory of controlled pharmacologic studies than is currently available. Similarly, much further study will be needed to determine the biological mechanisms by which the drug classes act in affective spectrum disorder. Fortunately, as mentioned earlier, knowledge of the actual mechanisms operating within the black box is not required for the present model. However, the model may help to focus the search for these mechanisms.

## PREDICTIONS

Predictions suggested by the model range from the limited to the general. We consider probable and possible forms of affective spectrum disorder together in what follows, but it should be noted that predictions regarding the former are offered with greater confidence.

1. Controlled studies will confirm a higher than average lifetime prevalence of major affective disorder in individuals with cataplexy, for which phenomenologic data at present are limited. More generally, all forms of affective spectrum disorder will show frequent comorbidity not only with major affective disorder but with one another.

2. Relatives of individuals with obsessive-compulsive disorder, cataplexy, migraine, and irritable bowel syndrome will display a higher prevalence of major affective disorder than relatives of control subjects. At present, family data in these disorders are limited.

More generally, relatives of individuals with all forms of affective spectrum disorder will demonstrate a higher prevalence of both major affective disorder and the other forms of affective spectrum disorder than relatives of control individuals. However, because the hypothesized common physiologic abnormality may not be inherited in all forms of affective spectrum disorder, these predictions are less secure than those in number 1.

3. Serotonin uptake inhibitors will prove effective in the treatment of attention deficit disorder with hyperactivity, migraine, and irritable bowel syndrome. Atypical agents will prove effective in cataplexy. Furthermore, new antidepressants and classes of antidepressants will likely prove effective in all forms of affective spectrum disorder, provided that their efficacy in major depression is clearly demonstrated to be superior to that of placebo and equal to that of reference antidepressants.

4. A common physiologic abnormality will be found in major depression, the other forms of affective spectrum disorder, and perhaps in several candidate disorders that have not yet met the drug response criteria required in the present analysis. This abnormality will be necessary (although probably not sufficient) for these disorders to occur.

It should be reiterated that an etiologic chain of many steps is required to produce the full clinical picture of any disorder. The model argues only that among these different chains of steps, there is at least one step that is the same for all forms of affective spectrum disorder. Antidepressants, whatever their other actions, will be found to act at this step to interrupt the etiologic chain of the disorder, thus ameliorating its symptoms.

If these predictions prove correct, affective spectrum disorder would emerge as one of the most widespread diseases of mankind. This development would underscore the potential importance of searching its many forms for their hypothesized common pathophysiology.

## REFERENCES

- Hess AF: Scurvy: Past and Present. Philadelphia, JB Lippincott, 1920
- Allison RS: Sea Diseases: The Story of a Great Natural Experiment in Preventive Medicine in the Royal Navy. London, John Bale Medical Publications, 1943
- Alarcon RD, Walter-Ryan WG, Rippetoe PA: Affective spectrum disorders. *Compr Psychiatry* 1987; 28:292-308
- Baldessarini RJ: *Chemotherapy in Psychiatry: Principles and Practice*, 2nd ed. Cambridge, Mass, Harvard University Press, 1985
- Ostrow D: The new generation antidepressants: promising innovations or disappointments? *J Clin Psychiatry* 1985; 46(10, section 2):25-30
- Schatzberg AF, Cole JO: *Manual of Clinical Psychopharmacology*. Washington, DC, American Psychiatric Press, 1986
- Rickels K, Chung HR, Csanalosi IB, et al: Alprazolam, diazepam, imipramine, and placebo in outpatients with major depression. *Arch Gen Psychiatry* 1987; 44:862-866
- Post RM, Uhde TW, Roy-Byrne PP, et al: Antidepressant effects of carbamazepine. *Am J Psychiatry* 1986; 143:29-34
- Chiarello RJ, Cole JO: The use of psychostimulants in general psychiatry: a reconsideration. *Arch Gen Psychiatry* 1987; 44: 286-295
- World Health Organization: *The International Classification of Diseases, 9th revision, Clinical Modification: ICD-9-CM*. Ann Arbor, Mich, Commission on Professional and Hospital Activities, 1978
- Hughes PL, Wells LA, Cunningham CJ, et al: Treating bulimia with desipramine: a placebo-controlled double-blind study. *Arch Gen Psychiatry* 1986; 43:182-186
- Barlow J, Blouin J, Blouin A, et al: Treatment of bulimia with desipramine: a double-blind crossover study. *Can J Psychiatry* 1988; 33:129-133
- Walsh BT, Roose SP, Wong IM, et al: Outcome of antidepressant treatment in bulimia, in CME Syllabus and Scientific Proceedings in Summary Form, 142nd Annual Meeting of the American Psychiatric Association. Washington, DC, APA, 1989
- Price WA, Babai MR: Antidepressant drug therapy for bulimia: current status revisited (letter). *J Clin Psychiatry* 1987; 48:385
- Walsh BT, Gladis M, Roose SP, et al: Phenelzine vs placebo in 50 patients with bulimia. *Arch Gen Psychiatry* 1988; 45:471-475
- Freeman CP: Drug treatment for bulimia and bulimia nervosa (abstract). *Psychopharmacology* 1988; 96(suppl):S124
- Enas GG, Pope HG Jr, Levine LR, et al: Fluoxetine in bulimia nervosa: double blind study, in New Research Program and Abstracts, 142nd Annual Meeting of the American Psychiatric Association. Washington, DC, APA, 1989
- Horne RL: Bupropion in the treatment of bulimia, in Abstracts of the First International Conference on Eating Disorders. New York, Montefiore Hospital, 1984
- Horne RL, Ferguson JM, Pope HG Jr, et al: Treatment of bulimia with bupropion: a multicenter controlled trial. *J Clin Psychiatry* 1988; 49:262-266
- Pope HG Jr, Hudson JL, Jonas JM, et al: Bulimia treated with imipramine: a placebo-controlled, double-blind study. *Am J Psychiatry* 1983; 140:554-558
- Agras WS, Dorian BG, Kirkley BG, et al: Imipramine in the treatment of bulimia: a double-blind controlled study. *Int J Eating Disord* 1987; 6:29-38
- Kaplan AS, Garfinkel PE, Garner DM: Bulimia treated with carbamazepine and imipramine, in New Research Program and Abstracts, 140th Annual Meeting of the American Psychiatric Association. Washington, DC, APA, 1987
- Mitchell JE, Pyle RL, Eckert ED, et al: Antidepressant versus group therapy for bulimia, in CME Syllabus and Scientific Proceedings in Summary Form, 142nd Annual Meeting of the American Psychiatric Association. Washington, DC, APA, 1989
- Kronig MH: Case report of successful treatment of bulimia with isocarboxazid (letter). *Am J Psychiatry* 1986; 143:551-552
- Kennedy SH, Piran N, Warsh JJ, et al: A trial of isocarboxazid in the treatment of bulimia. *J Clin Psychopharmacol* 1988; 8:391-396
- Nassr DG: Successful treatment of bulimia with nomifensine. *Am J Psychiatry* 1986; 143:373-374
- Pope HG Jr, Herridge PL, Hudson JL, et al: Treatment of bulimia with nomifensine. *Am J Psychiatry* 1986; 143:371-373
- Crane RA, Raskin V, Weiler M, et al: Nomifensine treatment of bulimia: results of an open trial. *Int J Eating Disord* 1987; 6:427-430
- Mitchell JE, Groat R: A placebo-controlled, double-blind trial of amitriptyline in bulimia. *J Clin Psychopharmacol* 1984; 4: 186-193
- Pope HG Jr, Hudson JL: Antidepressant drug therapy of bulimia: current status. *J Clin Psychiatry* 1986; 47:339-345
- Pope HG Jr, Hudson JL, Jonas JM: Antidepressant treatment of bulimia: preliminary experience and practical recommendations. *J Clin Psychopharmacol* 1983; 3:274-281



32. Roy-Byrne P, Gwirtsman HE, Edelstein CK, et al: Eating disorders and antidepressants. *J Clin Psychopharmacol* 1983; 3: 60-61
33. Brotman AW, Herzog DB, Woods SW: Antidepressant treatment of bulimia: the relationship between bingeing and depressive symptomatology. *J Clin Psychiatry* 1984; 45:7-9
34. Stewart JW, Walsh BT, Wright L, et al: An open trial of MAO inhibitors in bulimia. *J Clin Psychiatry* 1984; 45:217-219
35. Pope HG Jr, Hudson JI, Jonas JM, et al: Antidepressant treatment of bulimia: a two-year follow-up study. *J Clin Psychopharmacol* 1985; 5:320-327
36. Damlouji NF, Ferguson JM: Trazodone in the treatment of bulimic patients, in Abstracts of the First International Conference on Eating Disorders. New York, Montefiore Hospital, 1984
37. Ware MR, Lydiard RB: Trazodone in the treatment of bulimia. *J Clin Psychopharmacol* 1986; 6:253-254
38. Pope HG Jr, Keck PE Jr, McElroy SL, et al: A placebo-controlled study of trazodone in bulimia nervosa. *J Clin Psychopharmacol* 1989; 9:254-259
39. Sabine EJ, Yonace A, Farrington AJ, et al: Bulimia nervosa: a placebo-controlled double-blind therapeutic trial of mianserin. *Br J Clin Pharmacol* 1983; 15(suppl 2):195S-202S
40. Kahn RS, Westenberg HGM, Verhoeven WMA, et al: Effect of a serotonin precursor and uptake inhibitor in anxiety disorders: a double-blind comparison of 5-hydroxytryptophan, clomipramine and placebo. *Int Clin Psychopharmacol* 1987; 2: 33-45
41. Johnston DG, Troyer IE, Whitsett SF: Clomipramine treatment of agoraphobic women. *Arch Gen Psychiatry* 1988; 45: 453-459
42. Sheehan DV, Ballenger JC, Jacobson G: Treatment of endogenous anxiety with phobic, hysterical, and hypochondriacal symptoms. *Arch Gen Psychiatry* 1980; 37:51-59
43. Sheehan DV, Raj AB: Monoamine oxidase inhibitors, in Handbook of Anxiety Disorders. Edited by Last CG, Hersen M. New York, Pergamon Press, 1988
44. Evans L, Kenardy J, Schneider P, et al: Effect of a selective serotonin uptake inhibitor in agoraphobia with panic attacks: a double-blind comparison of zimeldine, imipramine and placebo. *Acta Psychiatr Scand* 1986; 73:49-53
45. Charney DS, Woods SW, Goodman WK, et al: Drug treatment of panic disorder: the comparative efficacy of imipramine, alprazolam, and trazodone. *J Clin Psychiatry* 1986; 47:580-586
46. Mavissakalian M, Perel J, Bowler K, et al: Trazodone in the treatment of panic disorder and agoraphobia with panic attacks. *Am J Psychiatry* 1987; 144:785-787
47. Klein DF: Delineation of two drug-responsive anxiety syndromes. *Psychopharmacologia* 1964; 53:397-408
48. Klein DF: Importance of psychiatric diagnosis in prediction of clinical drug effects. *Arch Gen Psychiatry* 1967; 16:118-125
49. Zitrin CM, Klein DF, Woerner MG: Treatment of agoraphobia with group exposure in vivo and imipramine. *Arch Gen Psychiatry* 1980; 37:63-72
50. Marks IM, Gray S, Cohen D, et al: Imipramine and brief therapist-aided exposure in agoraphobics having self-exposure homework. *Arch Gen Psychiatry* 1983; 40:153-162
51. Zitrin CM, Klein DF, Woerner MG, et al: Treatment of phobias, I: comparison of imipramine hydrochloride and placebo. *Arch Gen Psychiatry* 1983; 40:125-138
52. Telch MJ, Agras WS, Taylor B, et al: Combined pharmacological and behavioral treatment for agoraphobia. *Behav Res Ther* 1985; 23:325-335
53. Matuzas W: Alprazolam and imipramine in panic disorders, in CME Syllabus and Scientific Proceedings in Summary Form, 140th Annual Meeting of the American Psychiatric Association. Washington, DC, APA, 1987
54. Mavissakalian MR: Dose-response study: imipramine in panic disorder, in CME Syllabus and Scientific Proceedings in Summary Form, 141st Annual Meeting of the American Psychiatric Association. Washington, DC, APA, 1988
55. Lydiard RB, Ballenger JC: Antidepressants in panic disorder and agoraphobia. *J Affective Disord* 1987; 13:153-168
56. Gorman JM, Liebowitz MR, Fyer AJ, et al: An open trial of fluoxetine in the treatment of panic attacks. *J Clin Psychopharmacol* 1987; 7:329-332
57. Brady K, Zarzar M, Lydiard RB: Fluoxetine in panic disorder patients with imipramine-associated weight gain (letter). *J Clin Psychopharmacol* 1989; 9:66-67
58. Sheehan DV, Davidson J, Manschreck T, et al: Lack of efficacy of a new antidepressant (bupropion) in the treatment of panic disorder with phobias. *J Clin Psychopharmacol* 1983; 3:28-31
59. Muskin PR, Fyer AJ: Treatment of panic disorder. *J Clin Psychopharmacol* 1981; 1:81-90
60. Lydiard RB: Desipramine in agoraphobia with panic attacks: an open, fixed-dose study. *J Clin Psychopharmacol* 1987; 7: 258-260
61. Kalus O, Asnis GM, Cahn W, et al: Varying response to desipramine in panic disorder, in New Research Program and Abstracts, 142nd Annual Meeting of the American Psychiatric Association. Washington, DC, APA, 1989
62. Den Boer JA, Westenberg HG: Effect of a serotonin and nor-adrenaline uptake inhibitor in panic disorder: a double-blind comparative study with fluvoxamine and maprotiline. *Int Clin Psychopharmacol* 1988; 3:59-74
63. Den Boer JA, Westenberg HGM, Kamerbeek WDJ, et al: Effect of serotonin uptake inhibitors in anxiety disorders: a double-blind comparison of clomipramine and fluvoxamine. *Int Clin Psychopharmacol* 1987; 2:21-32
64. Berger P, Schoenbeck G, de Zwaan G, et al: Fluvoxamine in the treatment of panic attacks, an open pilot study (abstract). *Psychopharmacology* 1988; 96(suppl):S237
65. Servant D, Bailly D, Parquet PJ: Fluvoxamine in the treatment of panic disorder with obsessive-compulsive symptoms. *Am J Psychiatry* 1988; 9:1174-1175
66. Munjack DJ, Usigli R, Zulueta A, et al: Nortriptyline in the treatment of panic disorder and agoraphobia with panic attacks. *J Clin Psychopharmacol* 1988; 8:204-207
67. Sheehan DV: Current views on the treatment of panic and phobic disorders. *Drug Ther Hosp* 1982; 12:179-193
68. Lydiard RB: Successful utilization of maprotiline in a patient intolerant of tricyclics. *J Clin Psychopharmacol* 1987; 7:113-114
69. Karabanow O: Double-blind controlled study in phobias and obsessions. *J Int Med Res* 1977; 5(suppl 5):42-48
70. Jaskari MO: Observations on mianserin in the treatment of obsessive neurosis. *Curr Med Res Opin* 1980; 6:128-131
71. Marks I, Stern R, Mawson D, et al: Clomipramine and exposure for obsessive compulsive rituals. *Br J Psychiatry* 1980; 136:1-25
72. Montgomery SA: Clomipramine in obsessional neurosis: a placebo-controlled trial. *Pharm Med* 1980; 1:189-192
73. Thoren P, Asberg M, Chronholm B, et al: Clomipramine treatment of obsessive compulsive disorder, I: a controlled clinical trial. *Arch Gen Psychiatry* 1980; 37:1281-1289
74. Insel TR, Murphy DL, Cohen RM, et al: Obsessive-compulsive disorder: a double-blind trial of clomipramine and clorgyline. *Arch Gen Psychiatry* 1983; 40:605-612
75. Flament MF, Rapoport JL, Berg CJ, et al: Clomipramine treatment of childhood obsessive-compulsive disorder: a double-blind controlled study. *Arch Gen Psychiatry* 1985; 42:977-983
76. Mavissakalian M, Turner SM, Michelson L, et al: Tricyclic antidepressants in obsessive-compulsive disorder: antiobsessional or antidepressant agents? II. *Am J Psychiatry* 1985; 142:572-576
77. DeVeau-Geiss J, Landau P, Katz R: Preliminary results from a multicenter trial of clomipramine in obsessive-compulsive disorder. *Psychopharmacol Bull* 1989; 25:36-40
78. White L, Cole JO: Pharmacotherapy for obsessive compulsive disorder, in Handbook of Comparative Treatments for Adult Disorders. Edited by Bellack AS, Hersen M. New York, John Wiley & Sons, 1990
79. Annesley PT: Nardil response in a chronic obsessive compulsive. *Br J Psychiatry* 1969; 115:748

80. Jain VK, Swinson RP, Thomas JG: Phenelzine in obsessional neurosis. *Br J Psychiatry* 1970; 117:237-238
81. Isberg RS: A comparison of phenelzine and imipramine in an obsessive-compulsive patient. *Am J Psychiatry* 1981; 138: 1250-1251
82. Jenike MA, Surman OS, Cassem NH, et al: Monoamine oxidase inhibitors in obsessive-compulsive disorder. *J Clin Psychiatry* 1982; 44:131-132
83. Perse TL, Greist JH, Jefferson JW, et al: Fluvoxamine treatment of obsessive-compulsive disorder. *Am J Psychiatry* 1987; 144:1543-1548
84. Goodman WK, Price LH, Rasmussen SA, et al: Efficacy of fluvoxamine in obsessive-compulsive disorder: a double-blind comparison with placebo. *Arch Gen Psychiatry* 1989; 46:36-44
85. Vaisanen E, Ranta P, Nummikko-Pelkonen A, et al: Mianserin hydrochloride (Org GB 94) in the treatment of obsessional states. *J Int Med Res* 1977; 5:289-291
86. Ananth J, Solyom L, Solyom C, et al: Doxepin in the treatment of obsessive-compulsive neurosis. *Psychosomatics* 1975; 16: 185-187
87. Jenike MA, Vitagliano HL, Rabinowitz J, et al: Bowel obsessions responsive to tricyclic antidepressants in four patients. *Am J Psychiatry* 1987; 144:1347-1348
88. Jenike MA: Rapid response of severe obsessive-compulsive disorder to tranlycypromine. *Am J Psychiatry* 1981; 138: 1249-1250
89. Swinson RP: Response to tranlycypromine and thought stopping in obsessional disorder. *Br J Psychiatry* 1984; 144:425-427
90. Turner SM, Jacob RG, Beidel DC, et al: Fluoxetine treatment of obsessive-compulsive disorder. *J Clin Psychopharmacol* 1985; 5:207-212
91. Fontaine R, Chouinard G: An open clinical trial of fluoxetine in the treatment of obsessive-compulsive disorder. *J Clin Psychopharmacol* 1986; 6:98-101
92. Fontaine R, Chouinard G: Fluoxetine in the long-term maintenance treatment of obsessive compulsive disorder. *Psychiatr Annals* 1989; 19:88-91
93. Liebowitz MR, Hollander E, Schneier F, et al: Fluoxetine treatment of obsessive-compulsive disorder: an open clinical trial. *J Clin Psychopharmacol* 1989; 9:423-427
94. Jenike MA, Buttolph L, Baer L, et al: Open trial of fluoxetine in obsessive-compulsive disorder. *Am J Psychiatry* 1989; 146: 909-911
95. Frenkel AR: Fluoxetine in the treatment of obsessive-compulsive disorder—a long term study, in Abstracts of the World Federation of Societies of Biological Psychiatry Regional Congress on Biological Aspects of Non-Psychotic Disorders. Jerusalem, World Federation of Societies of Biological Psychiatry, 1989
96. Baxter LR Jr: Two cases of obsessive-compulsive disorder with depression responsive to trazodone. *J Nerv Ment Dis* 1985; 173:432-433
97. Prasad AJ: Efficacy of trazodone as an anti-obsessional agent. *Neuropsychobiology* 1986; 15(suppl 1):19-21
98. Lydiard RB: Obsessive-compulsive disorder successfully treated with trazodone. *Psychosomatics* 1986; 27:858-859
99. Kim SW: Trazodone in the treatment of obsessive-compulsive disorder: a case report. *J Clin Psychopharmacol* 1987; 7:278-279
100. Baxter LR Jr, Thompson JM, Schwartz JM, et al: Trazodone treatment response in obsessive-compulsive disorder—correlated with shifts in glucose metabolism in the caudate nuclei. *Psychopathology* 1987; 20(suppl 1):114-122
101. Hermesh H, Aizenberg D, Munitz H: Trazodone for clomipramine and lithium resistant obsessive compulsive disorder, in New Research Program and Abstracts, 142nd Annual Meeting of the American Psychiatric Association. Washington, DC, APA, 1989
102. Hussain MB, Ahad A: Treatment of obsessive compulsive neurosis. *Can Med Assoc J* 1970; 103:648-649
103. Snyder S: Amitriptyline therapy of obsessive-compulsive neurosis. *J Clin Psychiatry* 1980; 41:286-288
104. Ananth J, Pecknold JC, Van der Steen N, et al: Double blind comparative study of clomipramine and amitriptyline in obsessive neurosis. *Prog Neuropsychopharmacol Biol Psychiatry* 1981; 5:257-262
105. Prasad A: A double-blind study of imipramine versus zimeldine in treatment of obsessive-compulsive neurosis. *Pharmacopsychiatry* 1984; 17:61-62
106. Insel TR, Mueller EA, Alterman I, et al: Obsessive-compulsive disorder and serotonin: is there a connection? *Biol Psychiatry* 1985; 20:1174-1188
107. Kahn RS, Westenberg HC, Jolles J: Zimeldine treatment of obsessive-compulsive disorder: biological and neuropsychological aspects. *Acta Psychiatr Scand* 1984; 69:259-261
108. Fontaine R, Chouinard G, Iny L: An open clinical trial of zimeldine in the treatment of obsessive-compulsive disorder. *Curr Ther Res* 1985; 37:326-332
109. Freed A, Kerr TA, Roth M: The treatment of obsessional neurosis. *Br J Psychiatry* 1972; 120:590-591
110. Mavissakalian M, Michelson L: Tricyclic antidepressants in obsessive-compulsive disorder: antiobsessional or antidepressant agents? *J Nerv Ment Dis* 1983; 171:301-306
111. Pies R: Distinguishing obsessional from psychotic phenomena. *J Clin Psychopharmacol* 1984; 4:345-347
112. Volavka J, Neziroglu F, Yaryura-Tobias JA: Clomipramine and imipramine in obsessive-compulsive disorder. *Psychiatry Res* 1985; 14:83-91
113. Foa EB, Steketee G, Kozak MJ, et al: Effects of imipramine on depression and obsessive-compulsive symptoms. *Psychiatry Res* 1987; 21:123-136
114. Jenike MA, Armentano ME, Baer L: Disabling obsessive thoughts responsive to antidepressants. *J Clin Psychopharmacol* 1987; 7:33-35
115. Insel TR, Mueller EA, Gillin JC, et al: Tricyclic response in obsessive-compulsive disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 1985; 9:25-31
116. Zohar J, Insel TR: Obsessive-compulsive disorder: psychobiological approaches to diagnosis, treatment, and pathophysiology. *Biol Psychiatry* 1987; 22:667-687
117. Rapoport J, Leonard HL, Swedo SE: Treatment of childhood obsessive-compulsive disorder with clomipramine and desmethylimipramine: a double-blind crossover comparison (abstract). *Psychopharmacology* 1988; 96(suppl):S136
118. Aschenbach TM: *DSM-III* in light of empirical research on the classification of child psychopathology. *J Am Acad Child Psychiatry* 1980; 19:395-412
119. Garfinkel BD, Wender PH, Sloman L, et al: Tricyclic antidepressant and methylphenidate treatment of attention deficit disorder in children. *J Am Acad Child Psychiatry* 1983; 22: 343-348
120. Donnelly M, Zametkin AJ, Rapoport JL, et al: Treatment of childhood hyperactivity with desipramine: plasma drug concentration, cardiovascular effects, plasma and urinary catecholamine levels, and clinical response. *Clin Pharmacol Ther* 1986; 39:72-81
121. Baldessarini RJ, Wright V, et al: A double-blind placebo controlled study of desipramine in the treatment of ADD, I: efficacy. *J Am Acad Child Adolesc Psychiatry* 1989; 28:777-784
122. Zametkin A, Rapoport JL, Murphy DL, et al: Treatment of hyperactive children with monoamine oxidase inhibitors, I: clinical efficacy. *Arch Gen Psychiatry* 1985; 42:962-966
123. Casat CD, Pleasants DZ, Van Wyck Fleet J: A double-blind trial of bupropion in children with attention deficit disorder. *Psychopharmacol Bull* 1987; 23:120-122
124. Clay TH, Gualtieri T, Evans RW, et al: Clinical and neuropsychological effects of the novel antidepressant bupropion. *Psychopharmacol Bull* 1988; 24:143-148
125. Langer DH, Rapoport JL, Ebert MH, et al: Pilot trial of mianserin hydrochloride for childhood hyperactivity, in *The Psychobiology of Childhood: a Profile of Current Issues*. Edited by Greenhill LL, Shopsin B. New York, Spectrum Publications, 1984
126. Winsberg BS, Camp-Bruno JA, Vink J, et al: Mianserin phar-

- macokinetics and behavior in hyperkinetic children. *J Clin Psychopharmacol* 1987; 7:143-147
127. Cox WH Jr: An indication for use of imipramine in attention deficit disorder. *Am J Psychiatry* 1982; 139:1059-1060
  128. Rapoport JL, Zametkin A, Donnelly M, et al: New drug trials in attention deficit disorder. *Psychopharmacol Bull* 1985; 21: 232-236
  129. Guilleminault C, Mancuso J, Salva MAQ, et al: Viloxazine hydrochloride in narcolepsy: a preliminary report. *Sleep* 1986; 9:275-279
  130. Roselaar SE, Langdon N, Lock CB, et al: Selegiline in narcolepsy. *Sleep* 1987; 10:491-495
  131. Schacter M, Price PA, Parkes JD: Deprenyl in narcolepsy. *Lancet* 1979; 1:831-832
  132. Schrader H, Kaye K, Markset ACB, et al: The treatment of accessory symptoms in narcolepsy: a double-blind cross-over study of a selective serotonin re-uptake inhibitor (femoxetine) versus placebo. *Acta Neurol Scand* 1986; 74:297-303
  133. Passouant P, Baldy-Moulinier M, Aussilloux C: État de mal cataplectique au cours d'une maladie de Gélinau: influence de la clomipramine. *Société Française de Neurologie* 1970; 123: 56-60
  134. Parkes JD: Clomipramine (Anafranil) in the treatment of cataplexy. *J Int Med Res* 1973; 1:427-431
  135. Guilleminault C, Carskadon M, Dement WC: On the treatment of rapid eye movement narcolepsy. *Arch Neurol* 1974; 30:90-93
  136. Shapiro WR: Treatment of cataplexy with clomipramine. *Arch Neurol* 1975; 32:653-656
  137. Takahashi S: The action of tricyclics (alone or in combination with methylphenidate) upon several symptoms of narcolepsy, in Narcolepsy. Edited by Guilleminault C, Dement WC, Passouant P. New York, Spectrum Publications, 1976
  138. Schacter M, Parkes JD: Fluvoxamine and clomipramine in the treatment of cataplexy. *J Neurol Neurosurg Psychiatry* 1980; 43:171-174
  139. Langdon N, Shindler J, Parkes JD, et al: Fluoxetine in the treatment of cataplexy. *Sleep* 1986; 9:371-373
  140. Wyatt RJ, Fram DH, Buchbinder R, et al: Treatment of intractable narcolepsy with a monoamine oxidase inhibitor. *N Engl J Med* 1971; 285:987-991
  141. Hishikawa Y, Ida H, Nakai K, et al: Treatment of narcolepsy with imipramine (Tofranil) and desmethylinipramine (Pertofran). *J Neurol Sci* 1966; 3:453-461
  142. Passouant P, Halberg F, Genicot R, et al: La périodicité des accès narcoleptiques et le rythme ultradien du sommeil rapide. *Rev Neurol* 1969; 121:155-164
  143. Linnoila M, Simpson D, Skinner T: Characteristics of therapeutic response to imipramine in cataplectic men. *Am J Psychiatry* 1980; 137:237-238
  144. Godbout R, Montplaisir J: The effect of zimelidine, a serotonin-reuptake blocker, on cataplexy and daytime sleepiness of narcoleptic patients. *Clin Neuropharmacol* 1986; 9:46-51
  145. Schmidt HS, Clark RW, Hyman PR: Protriptyline: an effective agent in the treatment of the narcolepsy-cataplexy syndrome and hypersomnia. *Am J Psychiatry* 1977; 134:183-185
  146. Mitler MM, Shafor R, Hajdukovich R, et al: Treatment of narcolepsy: objective studies on methylphenidate, pemoline, and protriptyline. *Sleep* 1986; 9:260-264
  147. Gomersall JD, Stuart A: Amitriptyline in migraine prophylaxis: changes in pattern of attacks during a controlled clinical trial. *J Neurol Neurosurg Psychiatry* 1973; 36:684-690
  148. Couch JR, Hassanein RS: Amitriptyline in migraine prophylaxis. *Arch Neurol* 1979; 36:695-699
  149. Ziegler DK, Hurwitz A, Hassanein RS, et al: Migraine prophylaxis: a comparison of propranolol and amitriptyline. *Arch Neurol* 1987; 44:486-489
  150. Anthony M, Lance JW: Monoamine oxidase inhibition in the treatment of migraine. *Arch Neurol* 1969; 21:263-268
  151. Merikangas KR, Merikangas JR: Advances in the pharmacologic treatment of migraine (abstract). *Psychopharmacology* 1988; 96(suppl):S145
  152. Denaro A, Martucci N, Ruggieri S, et al: Headache and noradrenergic involvement: the effects of alpha<sub>2</sub>-stimulants and alpha<sub>2</sub>-antagonists. *Acta Psychiatr Scand* 1985; 72(suppl 320):20-25
  153. Monro P, Swade C, Coppen A: Mianserin in the prophylaxis of migraine: a double-blind study. *Acta Psychiatr Scand* 1985; 72(suppl 320):98-103
  154. Noone JF: Psychotropic drugs and migraine. *J Int Med Res* 1977; 5(suppl 1):66-71
  155. Langohr HD, Gerber WD, Koletzki E, et al: Clomipramine and metoprolol in migraine prophylaxis—a double-blind crossover study. *Headache* 1985; 25:107-113
  156. Heefner JD, Wilder RM, Wilson ID: Irritable colon and depression. *Psychosomatics* 1978; 19:540-547
  157. Greenbaum DS, Mayle JE, Vanegeren LE, et al: Effects of desipramine on irritable bowel syndrome compared with atropine and placebo. *Dig Dis Sci* 1987; 32:257-266
  158. Weiss KJ, Schwarz HG, Berrettini WH: Phenelzine treatment of depression with chronic diarrhea. *J Clin Psychiatry* 1982; 6:250-251
  159. Lydiard RB, Laraia MT, Howell EF, et al: Can panic disorder present as irritable bowel syndrome? *J Clin Psychiatry* 1986; 47:470-473
  160. Geisman RA, Alpers DH, Clouse RE: Response of irritable bowel syndrome to antidepressant therapy (abstract). *Gastroenterology* 1988; 94:A143
  161. Myren J, Groth H, Larssen SE, et al: The effect of trimipramine in patients with the irritable bowel syndrome. *Scand J Gastroenterol* 1982; 17:371-375
  162. Myren J, Lovland B, Larssen SE, et al: A double-blind study of the effect of trimipramine in patients with the irritable bowel syndrome. *Scand J Gastroenterol* 1984; 19:836-843
  163. Shrivastava RK, Siegel H: The role of tricyclics and benzodiazepine compounds in the treatment of irritable gut syndrome and peptic ulcer disease. *Psychopharmacol Bull* 1984; 20:616-621
  164. Diamond S: Amitriptyline in the treatment of gastrointestinal disorders. *Psychosomatics* 1964; 5:221-224
  165. Hislop IG: Psychological significance of the irritable colon syndrome. *Gut* 1971; 12:452-457
  166. Steinhart MJ, Young PY, Zarr ML: Therapeutic usefulness of amitriptyline in spastic colon syndrome. *Int J Psychiatry Med* 1981-1982; 11:45-57
  167. Gartrell N, Mosbacher D: A case report of irritable bowel syndrome treated with doxepin. *Am J Psychiatry* 1982; 139: 1351-1353
  168. Pies RW: Another case of doxepin for irritable bowel syndrome (letter). *Am J Psychiatry* 1983; 140:368-369
  169. Kasich AM: Management of emotional disorders, anxiety and depression, in patients with gastrointestinal disease. *Curr Ther Res* 1965; 9:542-547
  170. Biederman J, Herzog DB, Rivinus RM, et al: Amitriptyline in the treatment of anorexia nervosa: a double-blind placebo-controlled study. *J Clin Psychopharmacol* 1985; 5:10-16
  171. Halmi KA, Eckert ED, LaDu TJ, et al: Anorexia nervosa: treatment efficacy of cyproheptadine and amitriptyline. *Arch Gen Psychiatry* 1986; 43:177-181
  172. Hudson JL, Pope HG Jr, Jonas JM, et al: Treatment of anorexia nervosa with antidepressants. *J Clin Psychopharmacol* 1985; 5:17-23
  173. Kennedy SH, Piran N, Garfinkel PE: Monoamine oxidase inhibitor therapy for anorexia nervosa and bulimia: a preliminary trial of isocarboxazid. *J Clin Psychopharmacol* 1985; 5:279-285
  174. Davidson JRT, Kudler HS, Smith RD, et al: Treatment of posttraumatic stress disorder with amitriptyline and placebo. *Arch Gen Psychiatry* (in press)
  175. Frank JB, Kosten TR, Giller EL Jr, et al: A randomized clinical trial of phenelzine and imipramine for posttraumatic stress disorder. *Am J Psychiatry* 1988; 145:1289-1291
  176. Reist C, Kauffmann CD, Haier RJ, et al: A controlled trial of desipramine in 18 men with posttraumatic stress disorder. *Am J Psychiatry* 1989; 146:513-516
  177. Hogben GL, Cornfield RB: Treatment of traumatic war neu-



178. Levenson H, Lamman R, Rankin M: Traumatic war neurosis and phenelzine. *Arch Gen Psychiatry* 1982; 39:1345-1346
179. Walker JI: Chemotherapy of traumatic war stress. *Milit Med* 1982; 147:1029-1032
180. Shen WW, Park S: The use of monoamine oxidase inhibitors in the treatment of traumatic war neurosis: case report. *Milit Med* 1983; 148:430-431
181. van der Kolk BA: Psychopharmacological issues in posttraumatic stress disorder. *Hosp Community Psychiatry* 1983; 34: 683-691
182. Milanes FJ, Mack CN, Dennison J, et al: Phenelzine treatment of post-Vietnam stress syndrome. *VA Practitioner*, June 1984, pp 40-49
183. Davidson J, Walker JI, Kilts C: A pilot study of phenelzine in posttraumatic stress disorder. *Br J Psychiatry* 1987; 150:252-255
184. Lerer B, Bleich A, Kotler M, et al: Posttraumatic stress disorder in Israeli combat veterans. *Arch Gen Psychiatry* 1987; 44: 976-981
185. Shestatzky M, Greenberg D, Lerer B: A controlled trial of phenelzine in posttraumatic stress disorder. *Psychiatry Res* 1988; 24:149-155
186. Liebowitz MR, Gorman JM, Fyer AJ, et al: Pharmacotherapy of social phobia: an interim report of a placebo-controlled comparison of phenelzine and atenolol. *J Clin Psychiatry* 1988; 49:252-257
187. Benca R, Matuzas W, Al-Sadir J: Social phobia, MVP, and response to imipramine. *J Clin Psychopharmacol* 1986; 6:50-51
188. Kahn RJ, McNair DM, Lipman RS, et al: Imipramine and chlordiazepoxide in depressive and anxiety disorders. II: efficacy in anxious outpatients. *Arch Gen Psychiatry* 1986; 43: 79-85
189. Rickels K, Schweizer EE, Downing RW: Antidepressants in generalized anxiety disorders, in *New Research Program and Abstracts*, 140th Annual Meeting of the American Psychiatric Association. Washington, DC, APA, 1987
190. Messiha FS, Knopp W: A study of endogenous dopamine metabolism in Gilles de la Tourette's syndrome. *Ann Neurol* 1977; 2:69-70
191. Yaryura-Tobias JA, Neziroglu FA: Gilles de la Tourette syndrome: a new clinico-therapeutic approach. *Prog Neuropsychopharmacol* 1977; 1:335-338
192. Hoge SK, Biederman J: A case of Tourette's syndrome with symptoms of attention deficit disorder treated with desipramine. *J Clin Psychiatry* 1986; 47:478-479
193. Fras I, Karlavage J: The use of methylphenidate and imipramine in Gilles de la Tourette's disease in children. *Am J Psychiatry* 1977; 134:195-197
194. Fras I: Gilles de la Tourette's syndrome: effects of tricyclic antidepressants. *NY State J Med* 1978; 78:1230-1232
195. Caine ED, Polinsky RJ, Ebert MH, et al: Trial of chlorimipramine and desipramine for Gilles de la Tourette syndrome. *Ann Neurol* 1979; 5:305-306
196. Dillon DC, Salzman IJ, Schulsinger DA: The use of imipramine in Tourette's syndrome and attention deficit disorder: case report. *J Clin Psychiatry* 1985; 46:348-349
197. Sverd J: Imipramine treatment of panic disorder in a boy with Tourette's syndrome. *J Clin Psychiatry* 1988; 49:31-32
198. Riddle MA, Hardin MT, Cho SC, et al: Desipramine treatment of boys with attention-deficit hyperactivity disorder and tics: preliminary clinical experience. *J Am Acad Child Adolesc Psychiatry* 1988; 27:811-814
199. Riddle MA, Leckman JF, Hardin MT, et al: Fluoxetine treatment of obsessions and compulsions in patients with Tourette's syndrome (letter). *Am J Psychiatry* 1988; 145: 1173-1174
200. Feinmann C, Harris M, Cawley R: Psychogenic facial pain: presentation and treatment. *Br Med J* 1984; 288:436-438
201. Lascelles RG: Atypical facial pain and depression. *Br J Psychiatry* 1966; 112:651-659
202. Brownell LG, West P, Sweatman P, et al: Protriptyline in obstructive sleep apnea. *N Engl J Med* 1982; 307:1037-1042
203. Stepanski EJ, Conway WA, Young DK, et al: A double-blind trial of protriptyline in the treatment of sleep apnea syndrome. *Henry Ford Hosp Med J* 1988; 36:5-8
204. Whyte KF, Gould GA, Airlie AA, et al: Role of protriptyline and acetazolamide in the sleep apnea/hypopnea syndrome. *Sleep* 1988; 11:463-472
205. George CF, West P, Kryger MH: Trial of nomifensine in obstructive sleep apnea (OSA) (abstract). *Sleep Res* 1986; 15:123
206. Strober M, Salkin B, Burroughs J, et al: Validity of the bulimia-restrictor distinction in anorexia nervosa: parental personality characteristics and family psychiatric morbidity. *J Nerv Ment Dis* 1982; 170:345-351
207. Gershon ES, Hamovit JR, Schreiber JL, et al: Anorexia nervosa and major affective disorders associated in families: a preliminary report, in *Childhood Psychopathology and Development*. Edited by Guze SB, Earls FJ, Barrett JE. New York, Raven Press, 1983
208. Gwirtsman HE, Roy-Byrne P, Yager J, et al: Neuroendocrine abnormalities in bulimia. *Am J Psychiatry* 1983; 140:559-563
209. Hudson JI, Pope HG Jr, Jonas JM, et al: Phenomenologic relationship of eating disorders to major affective disorder. *Psychiatry Res* 1983; 9:345-354
210. Gershon ES, Schreiber JL, Hamovit JR, et al: Clinical findings in patients with anorexia nervosa and affective illness in their relatives. *Am J Psychiatry* 1984; 141:1419-1422
211. Hatsukami D, Eckert ED, Mitchell JE, et al: Affective disorder and substance abuse in women with bulimia. *Psychol Med* 1984; 14:701-714
212. Herzog DB: Are anorexic and bulimic patients depressed? *Am J Psychiatry* 1984; 141:1594-1597
213. Stern SL, Dixon KN, Nemzer E, et al: Affective disorder in the families of women with normal weight bulimia. *Am J Psychiatry* 1984; 141:1224-1227
214. Lee NF, Rush AJ, Mitchell JE: Depression and bulimia. *J Affective Disord* 1985; 9:231-238
215. Musisi S, Garfinkel P: Comparative dexamethasone suppression test measurements in bulimia, depression and normal controls. *Can J Psychiatry* 1985; 30:190-194
216. Piran N, Kennedy S, Garfinkel PE, et al: Affective disturbances in eating disorders. *J Nerv Ment Dis* 1985; 173:395-400
217. Viesselman JO, Roig M: Depression and suicidality in eating disorders. *J Clin Psychiatry* 1985; 46:118-124
218. Walsh BT, Roose SP, Glassman AH, et al: Bulimia and depression. *Psychosom Med* 1985; 47:123-131
219. Blouin A, McAffer V, Blouin J, et al: The incidence of depression in bulimia, in *Abstracts of the Second International Conference on Eating Disorders*. New York, Montefiore Hospital, 1986
220. Hudson JI, Pope HG Jr, Yurgelun-Todd D, et al: A controlled study of lifetime prevalence of affective and other psychiatric disorders in bulimic outpatients. *Am J Psychiatry* 1987; 144: 1283-1287
221. Laessle RG, Kittl S, Fichter MM, et al: Major affective disorder in anorexia nervosa and bulimia: a descriptive diagnostic study. *Br J Psychiatry* 1987; 151:785-789
222. Powers PS, Covert DL, Brightwell DR, et al: Other psychiatric disorders among bulimic patients. *Compr Psychiatry* 1988; 29:503-508
223. Hudson JI, Pope HG Jr, Keck PE Jr, et al: Treatment of bulimia nervosa with trazodone: short-term response and long-term follow-up. *Clin Neuropharmacol* 1989; 12(suppl 1): S38-S46
224. Logue CM, Crowe RR, Bean JA: A family study of anorexia nervosa and bulimia. *Compr Psychiatry* 1989; 30:179-188
225. Kassett JA, Gershon ES, Maxwell ME, et al: Psychiatric disorders in the first-degree relatives of probands with bulimia nervosa. *Am J Psychiatry* 1989; 146:1468-1471
226. Hudson JI, Pope HG Jr, Jonas JM, et al: Family history study of anorexia nervosa and bulimia. *Br J Psychiatry* 1983; 142: 133-138
227. Blouin J, Blouin A, Perez E, et al: Family history factors in bulimia, in *Abstracts of the Second International Conference*

- on Eating Disorders. New York, Montefiore Hospital, 1986
228. Hudson JL, Pope HG Jr, Jonas JM, et al: A controlled family history study of bulimia. *Psychol Med* 1987; 17:883-890
  229. Bowen RC, Kohout J: The relationship between agoraphobia and primary affective disorders. *Can J Psychiatry* 1979; 24: 317-322
  230. Dealy RS, Ishiki DM, Avery DH, et al: Secondary depression in anxiety disorders. *Compr Psychiatry* 1981; 22:612-618
  231. Raskin M, Pecke HVS, Dickman W, et al: Panic and generalized anxiety disorders: developmental antecedents and precipitants. *Arch Gen Psychiatry* 1982; 39:687-689
  232. Breier A, Charney DS, Heninger GR: Major depression in patients with agoraphobia and panic disorder. *Arch Gen Psychiatry* 1984; 41:1129-1135
  233. VanValkenburg C, Akiskal HS, Puzantian V, et al: Anxious depression: clinical, family history, and naturalistic outcome—comparisons with panic and major depressive disorders. *J Affective Disord* 1984; 6:67-82
  234. Uhde TW, Boulenger JP, Roy-Byrne PP, et al: Longitudinal course of panic disorder: clinical and biological considerations. *Prog Neuropsychopharmacol Biol Psychiatry* 1985; 9: 39-51
  235. Barlow DH, DiNardo PA, Vermilyea BB, et al: Co-morbidity and depression among the anxiety disorders: issues in diagnosis and classification. *J Nerv Ment Dis* 1986; 174:63-72
  236. Buller R, Maier W, Benkert O: Clinical subtypes in panic disorder: their descriptive and prospective validity. *J Affective Disord* 1986; 11:105-114
  237. Aronson TA, Logue CM: On the longitudinal course of panic disorder: developmental history and predictors of phobic complications. *Compr Psychiatry* 1987; 28:344-355
  238. Coryell W, Endicott J, Andreasen NC, et al: Depression and panic attacks: the significance of overlap as reflected in follow-up and family study data. *Am J Psychiatry* 1988; 145:293-300
  239. Lesser IM, Rubin RT, Pecknold JC, et al: Secondary depression in panic disorder and agoraphobia, I: frequency, severity, and response to treatment. *Arch Gen Psychiatry* 1988; 45: 437-443
  240. Stein MB, Tancer ME, Gelernter CS, et al: The longitudinal relationship between panic disorder and major depression, in Abstracts of the World Federation of Societies of Biological Psychiatry Regional Congress on Biological Aspects of Non-Psychotic Disorders. Jerusalem, World Federation of Societies of Biological Psychiatry, 1989
  241. Munjack DJ, Moss HB: Affective disorder and alcoholism in families of agoraphobics. *Arch Gen Psychiatry* 1981; 38:869-871
  242. Crowe RR, Noyes R Jr, Pauls DL, et al: A family study of panic disorder. *Arch Gen Psychiatry* 1983; 40:1065-1069
  243. Weissman MM: The epidemiology of anxiety disorders: rates, risks and familial patterns, in *Anxiety and the Anxiety Disorders*. Edited by Tuma AH, Maser J. Hillsdale, NJ, Lawrence Erlbaum Associates, 1985
  244. Sylvester CE, Hyde TS, Reichler RJ: Clinical psychopathology among children of adults with panic disorder, in *Relatives at Risk for Mental Disorder*. Edited by Dunner DL, Gershon ES, Barrett JE. New York, Raven Press, 1988
  245. Welner A, Reich T, Robins E, et al: Obsessive-compulsive neurosis: record, follow-up, and family studies, I: inpatient record study. *Compr Psychiatry* 1976; 17:527-539
  246. Rasmussen SA, Tsuang MT: Clinical characteristics and family history in *DSM-III* obsessive-compulsive disorder. *Am J Psychiatry* 1986; 143:317-322
  247. Rasmussen SA, Eisen JL: Clinical features and phenomenology of obsessive compulsive disorder. *Psychiatr Annals* 1989; 19: 67-73
  248. Swedo SE, Rapoport JL, Leonard H, et al: Obsessive-compulsive disorder in children and adolescents. *Arch Gen Psychiatry* 1989; 46:335-341
  249. Coryell W: Obsessive-compulsive disorder and primary unipolar depression: comparisons of background, family history, course, and mortality. *J Nerv Ment Dis* 1981; 169:220-224
  250. Insel TR, Hoover C, Murphy DL: Parents of patients with obsessive-compulsive disorder. *Psychol Med* 1983; 13:807-811
  251. McKeon P, Murray R: Familial aspects of obsessive-compulsive neurosis. *Br J Psychiatry* 1987; 151:528-534
  252. Lenane MC, Swedo S, Leonard H, et al: Obsessive-compulsive disorder in first degree relatives of obsessive-compulsive disorder children, in New Research Program and Abstracts, 141st Annual Meeting of the American Psychiatric Association. Washington, DC, APA, 1988
  253. Carlson GA, Cantwell DP: Unmasking masked depression in children and adolescents. *Am J Psychiatry* 1980; 137:445-449
  254. Biederman J, Munir K, Knee D, et al: High rate of affective disorders in probands with attention deficit disorder and in their relatives: a controlled family study. *Am J Psychiatry* 1987; 144:330-333
  255. Munir K, Biederman J, Knee D: Psychiatric comorbidity in patients with attention deficit disorder: a controlled study. *J Am Acad Child Adolesc Psychiatry* 1987; 26:844-848
  256. Biederman J, Faraone S, Keenan K, et al: Family-genetic patterns in clinically referred children and adolescents with attention deficit disorder, in Abstracts of the World Federation of Societies of Biological Psychiatry Regional Congress on Biological Aspects of Non-Psychotic Disorders. Jerusalem, World Federation of Societies of Biological Psychiatry, 1989
  257. Biederman J, Munir K, Knee D, et al: A family study of patients with attention deficit disorder and normal controls. *J Psychiatr Res* 1986; 20:263-274
  258. Lahey BB, Piacentini JC, McBurnett K, et al: Psychopathology in the parents of children with conduct disorder and hyperactivity. *J Am Acad Child Adolesc Psychiatry* 1988; 27:163-170
  259. Roth B, Nevsimalova S: Depression in narcolepsy and hypersomnia. *Schweiz Arch Neurol Neurochir Psychiatr* 1975; 116: 291-300
  260. Roy A: Psychiatric aspects of narcolepsy. *Br J Psychiatry* 1976; 128:562-565
  261. Zarcone VP, Fuchs HE: Psychiatric disorders and narcolepsy, in *Narcolepsy*. Edited by Guilleminault C, Dement WC, Pas-souant P. New York, Spectrum Publications, 1976
  262. Broughton R, Ghanem Q, Hishik Y, et al: Life effects of narcolepsy. *Can J Neurol Sci* 1981; 8:299-304
  263. Kales A, Soldatos CR, Bixler EO, et al: Narcolepsy-cataplexy, II: psychosocial consequences and associated psychopathology. *Arch Neurol* 1982; 39:169-171
  264. Krishnan RR, Volow MR, Miller PP, et al: Narcolepsy: preliminary retrospective study of psychiatric and psychosocial aspects. *Am J Psychiatry* 1984; 141:428-431
  265. Mouret J, Lemoine P, Sanchez P, et al: Treatment of narcolepsy with L-tyrosine. *Lancet* 1988; 2:1458-1459
  266. Kashiwagi T, McClure JN, Wetzel RD: Headache and psychiatric disorders. *Dis Nerv Syst* 1972; 33:659-663
  267. Marchesi C, De Ferri A, Petrolini N, et al: Prevalence of migraine and muscle tension headache in depressive disorders. *J Affective Disord* 1989; 16:33-36
  268. Sandler M, Jarman J, Glover V: Endogenous depression in a migraine clinic population, identification by use of the oral tyramine test, in Abstracts of the World Federation of Societies of Biological Psychiatry Regional Congress on Biological Aspects of Non-Psychotic Disorders. Jerusalem, World Federation of Societies of Biological Psychiatry, 1989
  269. Liss JL, Alpers D, Woodruff RA Jr: The irritable colon syndrome and psychiatric illness. *Dis Nerv Syst* 1973; 34:151-157
  270. Fava G, Pavan L: Large bowel disorders, II: psychopathology and alexithymia. *Psychother Psychosom* 1976/1977; 27:100-105
  271. Young SJ, Alpers DH, Norland CC, et al: Psychiatric illness and the irritable bowel syndrome: practical implications for the primary physician. *Gastroenterology* 1976; 70:162-166
  272. Latimer P, Sarna S, Campbell D: Colonic motor and myoelectrical activity: a comparative study of normal subjects, psychoneurotic patients, and patients with irritable bowel syndrome. *Gastroenterology* 1981; 80:893-901
  273. Wender PH, Kalm M: Prevalence of attention deficit disorder,

- residual type, and other psychiatric disorders in patients with irritable colon syndrome. *Am J Psychiatry* 1983; 140:1579–1582
274. Fossey MD, Lydiard RB, Marsh WH, et al: Psychiatric morbidity in irritable bowel syndrome, in *New Research Program and Abstracts*, 142nd Annual Meeting of the American Psychiatric Association. Washington, DC, APA, 1989
  275. Leckman JF, Merikangas KR, Pauls DL, et al: Anxiety disorders and depression: contradictions between family study data and *DSM-III* conventions. *Am J Psychiatry* 1983; 140:880–882
  276. Gittleson NL: The fate of obsessions in depressive psychosis. *Br J Psychiatry* 1966; 112:705–708
  277. Alessi NE, Magen J: Comorbidity of other psychiatric disturbances in depressed, psychiatrically hospitalized children. *Am J Psychiatry* 1988; 145:1582–1584
  278. Garvey MJ, Tollefson GD, Schaffer CG: Migraine headaches and depression. *Am J Psychiatry* 1984; 141:986–988
  279. Merikangas KR, Risch NJ, Merikangas JR, et al: Migraine and depression: association and familial transmission. *J Psychiatr Res* 1988; 22:119–129
  280. Boyd JH, Burke JD, Gruenberg E, et al: Exclusion criteria of DSM-III: a study of co-occurrence of hierarchy-free symptoms. *Arch Gen Psychiatry* 1984; 41:983–989
  281. Merikangas KR, Angst J, Isler H: Migraine and depression: the Zurich cohort, in *New Research Program and Abstracts*, 142nd Annual Meeting of the American Psychiatric Association. Washington, DC, APA, 1989
  282. Karno M, Golding JM, Sorenson SB, et al: The epidemiology of obsessive-compulsive disorder in five US communities. *Arch Gen Psychiatry* 1988; 45:1094–1099
  283. Anderson JC, Williams S, McGee R, et al: DSM-III disorders in preadolescent children. *Arch Gen Psychiatry* 1987; 44:69–76
  284. Crisp AH, Kalucy RS, McGuinness B, et al: Some clinical, social and psychological characteristics of migraine subjects in the general population. *Postgrad Med J* 1977; 53:691–697
  285. Leckman JF, Weissman MM, Merikangas KR, et al: Panic disorder and major depression: increased risk of depression, alcoholism, panic, and phobic disorders in families of depressed probands with panic disorder. *Arch Gen Psychiatry* 1983; 40:1055–1060
  286. Weissman MM, Leckman JF, Merikangas KR, et al: Depression and anxiety disorders in parents and children: results from the Yale family study. *Arch Gen Psychiatry* 1984; 41:845–852
  287. Gershon ES, McKnew D, Cytryn L, et al: Diagnoses in school-age children of bipolar affective disorder patients and normal controls. *J Affective Disord* 1985; 8:283–291
  288. Kashani JH, Burk JP, Horwitz B, et al: Differential effect of subtype of parental major affective disorder on children. *Psychiatry Res* 1985; 15:195–204
  289. Grigoriou-Serbanescu M, Christodorescu D, Jipescu I, et al: Psychopathology in children aged 10–17 of bipolar parents: psychopathology rate and correlates of the severity of the psychopathology. *J Affective Disord* 1989; 16:167–179
  290. Orvaschel H: Comorbidity of attention deficit disorder and depression, in *Abstracts of the World Federation of Societies of Biological Psychiatry Regional Congress on Biological Aspects of Non-Psychotic Disorders*. Jerusalem, World Federation of Societies of Biological Psychiatry, 1989
  291. Pitman RK, Green RC, Jenike MA, et al: Clinical comparison of Tourette's disorder and obsessive-compulsive disorder. *Am J Psychiatry* 1987; 144:1166–1171
  292. Sheehan DV, Sheehan KH: The classification of anxiety and hysterical states, part I: historical review and empirical delineation. *J Clin Psychopharmacol* 1982; 2:235–244
  293. Katon W: Panic disorder and somatization: review of 55 cases. *Am J Med* 1984; 77:101–106
  294. Mellman TA, Uhde TW: Obsessive-compulsive symptoms in panic disorder. *Am J Psychiatry* 1987; 144:1573–1576
  295. Yeragani VK, Pohl R, Balon R, et al: Migraine and panic disorder (letter). *J Clin Psychopharmacol* 1988; 8:148
  296. Schotte DE, Stunkard AJ: Bulimia vs bulimic behaviors on a college campus. *JAMA* 1987; 258:1213–1215
  297. Linet MS, Stewart WF: Migraine headache: epidemiologic perspectives. *Epidemiol Rev* 1984; 6:107–139
  298. Thompson WG, Heaton KW: Functional bowel disorders in apparently healthy people. *Gastroenterology* 1980; 79:283–288
  299. Lewis A: Melancholia: a clinical survey of depressive states. *J Ment Sci* 1934; 80:277–378
  300. Janet P: *Les Obsessions et la Psychasthénie*. Paris, Félix Alcan, 1903
  301. Pope HG Jr, Hudson JI, Miale JP: Bulimia in the late nineteenth century: the observations of Pierre Janet. *Psychol Med* 1985; 15:739–743
  302. Klein DF, Gittelman R, Quitkin F, et al: *Diagnosis and Drug Treatment of Psychiatric Disorders: Adults and Children*, 2nd ed. Baltimore, Williams & Wilkins, 1980
  303. Munjack DJ, Rebal R, Shaner R, et al: Imipramine versus propranolol for the treatment of panic attacks: a pilot study. *Compr Psychiatry* 1985; 26:80–89
  304. Walton J: *Brain's Diseases of the Nervous System*. Oxford, Oxford University Press, 1985
  305. Spiro HM: *Clinical Gastroenterology*, 3rd ed. New York, Macmillan, 1983
  306. Buigues J, Vallejo J: Therapeutic response to phenelzine in patients with panic disorder and agoraphobia with panic attacks. *J Clin Psychiatry* 1987; 48:55–59
  307. Biederman J, Gastfriend DR, Jellinek MS: Desipramine in the treatment of children with attention deficit disorder. *J Clin Psychopharmacol* 1986; 6:359–363
  308. Couch JR, Ziegler DK, Hassanein R: Amitriptyline in the prophylaxis of migraine. *Neurology* 1976; 26:121–127
  309. Klein DF: The pharmacological validation of psychiatric diagnosis, in *The Validity of Psychiatric Diagnosis*. Edited by Robbins LN, Barrett JE. New York, Raven Press, 1989
  310. Liebowitz MR, Quitkin FM, Stewart JW, et al: Antidepressant specificity in atypical depression. *Arch Gen Psychiatry* 1988; 45:129–137



# Irritable Bowel Syndrome and Psychiatric Illness

Edward A. Walker, M.D., Peter P. Roy-Byrne, M.D., and Wayne J. Katon, M.D.

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*Psychiatric illnesses such as mood, anxiety, and somatization disorders share many common features with irritable bowel syndrome. The authors review recent developments in the definition of irritable bowel syndrome and its relationship to psychiatric illness, discuss the diagnostic validity of irritable bowel syndrome from several perspectives, and offer a pathophysiological model of irritable bowel syndrome that integrates many of the biological and psychosocial findings of earlier studies. Psychiatric evaluation appears to be an important factor in the diagnosis and treatment of patients with irritable bowel syndrome.* (Am J Psychiatry 1990; 147:565-572)

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Irritable bowel syndrome is the most common gastrointestinal disorder encountered by primary care physicians and gastroenterologists: prevalence figures range from 13% to 52% of new referrals to gastrointestinal clinics (1, 2). Despite the high prevalence of this disorder, however, there is incomplete agreement on its definition and its status as a valid diagnostic entity.

One of the more striking features of this syndrome is the frequent finding of associated psychiatric illness, especially mood, anxiety, and somatization disorders. Studies have suggested that 54%–100% of patients with irritable bowel syndrome may have associated psychiatric illness (3–8). Although the psychological characteristics and psychiatric illnesses of patients with irritable bowel syndrome have been extensively reviewed (9–13), the nature of this association has not been well established.

The clarification of this relationship is important. Methodological critiques of other heterogeneous syndromes such as premenstrual syndrome (14) have demonstrated the importance of careful definition and delimitation from other disorders, particularly psychiatric conditions, to avoid the problems inherent in studying heterogeneous populations.

There are at least two possible ways that irritable

bowel syndrome and psychiatric illness could be related. 1) Irritable bowel syndrome could be a precursor of psychiatric disorders. This view holds that psychiatric symptoms develop secondary to the stress of a chronic physical disease (a "somatopsychic" model). 2) Irritable bowel syndrome could be an epiphenomenon or forme fruste of psychiatric disorders (a "psychosomatic" model). This view is compatible with the idea that symptoms like those of irritable bowel syndrome are common in the general population and, when amplified by psychiatric illness, reach the status of a disease or disorder (15).

To further evaluate the relationship of irritable bowel syndrome and psychiatric illness, we will explore four questions: 1) What is known about the definition and diagnostic validity of irritable bowel syndrome? 2) How are irritable bowel syndrome and psychiatric symptoms related? 3) Is there a pathophysiological model for irritable bowel syndrome that includes a neurobiological component? and 4) What is the role of the psychiatrist in the evaluation and treatment of patients with irritable bowel syndrome?

## WHAT IS IRRITABLE BOWEL SYNDROME?

It is not easy to define what irritable bowel syndrome is but easy to say what it is not. Since its initial description by Powell in 1820, it has been described by 30 different names, each reflecting changing models of organic and psychological etiology (9). Irritable bowel syndrome has been considered a diagnosis of exclusion, assigned to patients whose symptoms lack sufficient evidence for an organic etiology.

To avoid the trap of heterogeneity inherent in diagnosis by exclusion, Manning et al. (16) suggested the use of operationalized diagnostic criteria to discriminate patients with irritable bowel syndrome from patients with organic disease. These criteria were further refined by Thompson and Heaton (17), Drossman et al. (15), Whitehead and Schuster (18), and, most recently, by an international congress on gastroenterology in Rome (Drossman, 1988, personal communication). The congress defined irritable bowel syndrome as follows:

Continuous or recurrent symptoms of:

1. Abdominal pain, relieved with defecation or associated with change in frequency or consistency of stool, and/or

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Received April 25, 1989; revisions received July 12 and Sept. 6, 1989; accepted Sept. 18, 1989. From the Department of Psychiatry and Behavioral Sciences, Division of Consultation-Liaison, University of Washington. Address reprint requests to Dr. Walker, Department of Psychiatry and Behavioral Sciences, Division of Consultation-Liaison, University of Washington, Seattle, WA 98195.

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2. Disturbed defecation (two or more of):
  - a) altered stool frequency,
  - b) altered stool form (hard or loose/watery),
  - c) altered stool passage (straining or urgency, feeling of incomplete evacuation),
  - d) passage of mucus,
 usually with
3. Bloating or feeling of abdominal distension.

Noting the high prevalence of emotional distress in patients with irritable bowel syndrome, Whitehead et al. (18, 19) suggested that psychological criteria also be incorporated into the definition. Additionally, they proposed the need for two distinct sets of criteria, one for research and another for clinical use. Research diagnostic criteria would select a specific, narrowly defined, homogeneous population for epidemiologic and treatment outcome studies, but a more sensitive, broad set of clinical criteria could be used for treatment in outpatient clinics.

Although irritable bowel syndrome was first recognized as a disorder of the colon, some gastroenterologists feel that because the motility and functioning of various parts of the gastrointestinal tract are more alike than dissimilar, irritable bowel syndrome may represent a continuum of similar gastrointestinal diagnoses with symptoms that are site-specific depending on the level of involvement (20–22). Thus, patients with esophageal symptoms, delayed emptying syndromes, and proctalgia fugax may have “irritable-bowel-syndrome-like” diseases and need to be studied with the same careful methodological consideration.

The existence of diagnostic criteria for irritable bowel syndrome, however, does not imply the validity of the diagnosis, and if it is a valid diagnosis we should be able to distinguish it from other medical and psychiatric illnesses.

#### IS IRRITABLE BOWEL SYNDROME A VALID DIAGNOSIS?

By definition, a syndrome is a collection of symptoms and signs that co-vary. How unique is the set of symptoms and signs of irritable bowel syndrome? How much overlap is there with other medical or psychiatric illness?

Patients with irritable bowel syndrome manifest some symptoms that clearly suggest gastrointestinal distress (pain, distention, flatus, and urgency), but they also show features of autonomic arousal that are common in mood and anxiety disorders, such as weakness, fatigue, palpitations, nervousness, dizziness, headache, hand tremor, back pain, sleep disturbance, and symptoms of sexual dysfunction (2, 23–26). It is the combination of these gastrointestinal and psychiatric symptoms that appears to separate patients with irritable bowel syndrome from other patients with pure gastrointestinal or psychiatric illness.

Very little is known about the family histories of

patients with irritable bowel syndrome. Although there have been no genetic studies, some studies suggested that the symptoms may run in families. Two-thirds of the parents and half of the siblings of children with recurrent abdominal pain suffered abdominal pain themselves (27, 28). However, this finding may represent a learned phenomenon rather than a genetic phenomenon, since the parents of patients with irritable bowel syndrome may have paid more attention to their bowel problems (29).

Irritable bowel syndrome appears to have its onset in late adolescence, sometimes before age 15, and affects twice as many females as males (2). The majority of patients are between 20 and 40 years old, and the condition is rare after age 60 (12). Studies have found symptoms like those of irritable bowel syndrome in 10%–20% of the general population (15, 17, 30), including individuals who do not seek medical care for irritable bowel syndrome (15, 31). The early age at onset (32, 33), female predominance (34, 35), and lower prevalence in the elderly (32) are similar to characteristics seen in patients with panic disorder and major depression.

Irritable bowel syndrome appears to be a chronic condition marked by waxing and waning symptoms with occasional exacerbations. One-third of the adults with the diagnosis of irritable bowel syndrome experienced similar symptoms as children (2), and in children with recurrent abdominal pain (which may be a precursor of irritable bowel syndrome), gastrointestinal symptoms tend to remain chronic, although their severity varies over time (36, 37). This is consistent with the chronicity of anxiety disorders and somatization disorder, both of which appear to be frequently associated with irritable bowel syndrome.

Are there physiological markers that are characteristic of patients with irritable bowel syndrome? Despite the general agreement that irritable bowel syndrome is a disorder of intestinal motility, studies have varied in their control of critical methodological variables, and no characteristic physiological marker has been found. Compared with control subjects, many patients with irritable bowel syndrome appear to have a higher proportion of “slow” (3 cycles/min) myoelectric activity in the distal colon (38–42). This abnormality in electrical activity is unrelated to bowel habits or diet and persists despite symptom remission (43). However, many patients who do not have irritable bowel syndrome also have this abnormality, and some patients with irritable bowel syndrome have both the symptoms and the motility marker, but they do not correlate. This variation in the basic electrical rhythm of the gut may represent a physiological “trait” that confers vulnerability in the presence of additional factors, perhaps from the CNS.

It is not clear, however, that this abnormal myoelectric activity is directly related to symptoms of irritable bowel syndrome. Although it seems to be associated with and perhaps regulates slower frequency contractions of the colon that are nonpropulsive and segmen-

TABLE 1. Studies of Coexisting Gastrointestinal and Psychiatric Symptoms in Patients With Irritable Bowel Syndrome

Study	Number of Subjects	Number of Control Subjects	Psychiatric Measure	Subjects With Coexisting Psychiatric and Gastrointestinal Disorders							
				Anxiety		Affective		Hysteria		Other	
				N	%	N	%	N	%	N	%
Liss et al. (3)	25	0	RDC	6	24	2	8	7	28	8	32
Young et al. (4)	29	33	RDC	1	4	5	17	5	17	10	35
Fava and Pavan (5)	20	40	RDC	1	5	9	45	3	15	1	5
Latimer et al. (6)	16	17	RDC	3	19	5	31	2	13	6	32
Wender and Kalm (7) <sup>a</sup>	22	0	RDC	3	14	11	50	—	—	7	32
Ford et al. (8)	48	16	RDC	—	—	—	—	—	—	—	—
										26	54

<sup>a</sup>Some patients had more than one diagnosis, but total percent reflects the percent of the entire sample with any diagnosis.

tal and impede normal peristaltic fecal movement (39), these slower frequency contractions are not more frequent at rest in patients with irritable bowel syndrome than in normal subjects. However, in patients with irritable bowel syndrome they become more frequent following infusions of cholecystokinin and pentagastrin (39), food ingestion (40), or balloon distention of the colon (44) and seem to be associated with pain in patients with irritable bowel syndrome who have prominent meal-associated symptoms (45). Some investigators (46, 47) have shown abnormalities in small bowel motility as well, suggesting involvement of levels of the gastrointestinal tract outside the colon. Thus, patients with irritable bowel syndrome may have a sensitive gastrointestinal tract that responds in an exaggerated way to stimuli which normally regulate motor activity.

In addition, patients with irritable bowel syndrome may experience pain differently, both quantitatively and qualitatively. Patients with irritable bowel syndrome report gastrointestinal pain sooner and more intensely than control subjects when subjected to stepwise colonic balloon distention (44, 48, 49), although the methodology of these studies has been criticized (50). Furthermore, two studies (49, 51) have found that patients with irritable bowel syndrome experience pain in unusual, atypical abdominal sites (upper abdomen) as well as in extra-abdominal sites.

Just as there have been no definitive biological markers for irritable bowel syndrome, there do not appear to be any characteristic psychological markers either. Although patients with irritable bowel syndrome are psychologically more distressed than normal subjects, they do not have a common psychological profile on standard psychological assessment instruments such as the MMPI.

The recent establishment of diagnostic criteria for irritable bowel syndrome should improve the chances of more accurately identifying the characteristics of the syndrome. We accept the imprecision of previous definitions and will attempt to examine clinical features of irritable bowel syndrome as they were defined in each study.

What is the evidence that irritable bowel syndrome

and psychiatric symptoms occur at the same time in the same individual?

#### PSYCHIATRIC ILLNESS IN PATIENTS WITH IRRITABLE BOWEL SYNDROME

Studies of coexisting gastrointestinal and psychiatric symptoms in patients with irritable bowel syndrome have been difficult to compare due to methodological differences. However, more recent studies show a consistent trend toward substantial psychiatric illness in this population, as illustrated in table 1.

Interpretation of these studies is problematic. First, Research Diagnostic Criteria prevent the simultaneous diagnosis of anxiety disorders when a primary affective illness diagnosis is made, and since estimates suggest that 25%–33% of patients with depression may also suffer from a concurrent anxiety disorder (52), the prevalence of anxiety diagnoses is most likely considerably higher than these studies suggest. Second, some patients receiving the diagnosis of "hysteria" (who would probably now meet criteria for somatization disorder) may well have had panic disorder, since the Epidemiologic Catchment Area data have demonstrated considerable overlap of symptom criteria between panic disorder and somatization disorder (53). Nonetheless, the total percentage of patients with psychopathology is very high in groups with irritable bowel syndrome.

Although there is evidence for an association, what is the nature of this relationship?

#### *Hypothesis 1: Irritable Bowel Syndrome Is a Precursor of Psychiatric Illness*

The essential feature of the somatopsychic hypothesis is that psychiatric symptoms develop as a consequence of or as a reaction to the chronic stress of coping with gastrointestinal disease. This is similar to the situation in which depression develops secondarily to a medical disease such as cancer. For this hypothesis to be valid, two conditions must be satisfied. 1) The timing of the symptoms of irritable bowel syndrome must precede the development of psychiatric symptoms. 2)



There should be evidence that other gastrointestinal disorders can create similar psychiatric sequelae.

We could not find any studies to support the idea that symptoms of irritable bowel syndrome temporally precede mood or anxiety symptoms. However, there have been studies of other syndromes frequently considered in the differential diagnostic assessment of irritable bowel syndrome. Although ulcerative colitis has been considered one of the classical psychosomatic diseases, patients with this disorder are no more likely to have current or lifetime psychiatric diagnoses than medically ill control subjects (54). Conversely, patients with Crohn's disease have been found to have a significantly higher prevalence of psychiatric illness than medically ill control subjects (55). However, Crohn's disease is more likely than ulcerative colitis to lead to a course of treatment involving multiple surgeries and colostomy, chronic steroid use, and hyperalimentation. This may lead to a higher prevalence of secondary psychiatric illness in patients with this disorder. Although patients with Crohn's disease have a higher prevalence of psychiatric illness than patients with ulcerative colitis, the prevalence is still far below that of patients with irritable bowel syndrome.

It would appear from these studies that the magnitude of the psychiatric illness found in patients with irritable bowel syndrome cannot be explained simply as a reaction to the chronic stress of physical disease.

#### *Hypothesis 2: Irritable Bowel Syndrome Is a Forme Fruste of Psychiatric Illness*

Could irritable bowel syndrome be a somatic expression of psychiatric illness? This psychosomatic or psychophysiological hypothesis asserts that the gastrointestinal manifestations of irritable bowel syndrome are either secondary somatic reactions to psychological distress or amplifications of mildly aversive symptoms that are normally present but are reified into a "disorder" by psychological factors. Essential features of this hypothesis are that 1) the timing of symptoms must be preceded by psychological distress and psychiatric illness, 2) these a priori psychological factors must affect the way symptoms are manifested or experienced in irritable bowel syndrome, and 3) effective treatments for the underlying psychiatric illness should have efficacy in removing the gastrointestinal symptoms as well.

*The timing of symptoms.* Although there are many studies of the psychological characteristics of patients with irritable bowel syndrome (3, 4, 8, 56–59), only a few studies (3, 4, 8) have reliably measured the relative timing of psychiatric symptoms and irritable bowel syndrome symptoms. These studies suggested that the onset of psychiatric illness frequently precedes the onset of gastrointestinal symptoms in the majority of patients with functional gastrointestinal disorders.

Preliminary data from our ongoing study of psychiatric epidemiology in patients with irritable bowel syndrome support these findings. When a consecutive

sample of 13 patients with irritable bowel syndrome was compared with a similar sample of 10 patients diagnosed with inflammatory bowel disease in a prospective design with structured psychiatric interviewing (the National Institute of Mental Health Diagnostic Interview Schedule), patients with irritable bowel syndrome were more likely than control subjects to have had a history of anxiety (85% versus 20%;  $p < 0.004$ , Fisher exact test) and somatization disorder (77% versus 0%;  $p < 0.001$ , Fisher exact test) but no statistical difference in major depression (54% versus 20%, n.s., Fisher exact test).

*Do psychological factors affect symptom presentation?* Most studies of the premorbid psychological characteristics of patients with irritable bowel syndrome have had retrospective designs, which can be flawed by recall bias and the use of tertiary care populations (patients with irritable bowel syndrome in gastrointestinal clinics or those referred to psychiatric consultation). The complex interaction of physical illness, personal and family responses to illness, and learned illness behavior can be difficult to disentangle. Nevertheless, a number of studies have examined the psychosocial histories of patients with irritable bowel syndrome and have suggested that many of the features of irritable bowel syndrome may be more characteristic of the patient's coping and adaptation patterns than of the disease.

Many people have symptoms like those of irritable bowel syndrome but do not report them to physicians (15). Conversely, patients with irritable bowel syndrome are more likely to complain of other nongastrointestinal symptoms and have higher rates of physician utilization than patients without irritable bowel syndrome (24). These patients also have a higher proportion of abnormal personality patterns, greater illness behaviors, lower positive stressful life event scores, less coping capability, and more frequent experiences of symptoms causing life disruption than people with irritable bowel syndrome who do not seek care (60).

Lowman et al. (29) reported that people admitting to symptoms of irritable bowel syndrome (patients and nonpatients) were significantly more likely than normal control subjects to have had childhood histories of frequent visits to the doctor; poorer general health; more headaches, stomachaches, and pain associated with bowel problems; greater parental attention to illness; more loss and separation; and more frequent school absences. Many of these same characteristics are commonly found in patients who have high rates of use of primary care (61), who often have chronic mixed anxiety and depression complaints. Tyrer (62) has argued that such subsyndromal complaints are better understood by the abandoned concept of neurosis, which also suggests maladaptive personality traits. Perhaps people with irritable bowel syndrome who frequent clinics have premorbid personality characteristics that modulate the way they perceive and become distressed by physiological cues, resulting in depres-

sion, anxiety symptoms, and more health-care-seeking behavior. Both depression and anxiety have been demonstrated to interfere with habituation to aversive symptoms such as tinnitus and pain, thus amplifying distress and disability (63).

**Treatment considerations.** Do treatments that are effective for psychiatric illness also reduce the symptoms of irritable bowel syndrome? Unfortunately, previous studies have contained substantial methodological flaws that make comparison difficult. Klein (64) reviewed more than 100 pharmacological treatment studies and found only 43 placebo-controlled double-blind studies, none of which rigorously met the methodological criteria essential for establishing efficacy. Placebo response rates ranged from 20% to 70%. Many treatment studies also lacked specific outcome criteria and measures of functional change before and after treatment. Some treatments failed to "cure" irritable bowel syndrome but resulted in a decrease in certain symptom complaints or a reduction in social and occupational disability.

A few of the pharmacological studies are less problematic than others, however. Controlled studies of antidepressants (65–70) have yielded equivocal results but suggest that these agents may be effective in some patients by reducing gastrointestinal symptoms and pain. Controlled trials of anxiolytics (71–73) have likewise been ambiguous but seem to offer less promise. However, Lydiard et al. (74) described five patients with irritable bowel syndrome whose symptoms resembled those of panic disorder in periodicity and associated symptoms who responded to treatment with alprazolam.

There are very few well-designed studies of response to behavioral or psychotherapeutic treatment interventions. The provision of suitable control therapies and the operational definition of psychotherapeutic technique are difficult. Studies of combined psychotherapy with a benzodiazepine (75), time-limited group psychotherapy (76), combined medical and psychotherapeutic treatments (25, 77), and hypnotherapy (78) have suggested some potential advantage to multimodal therapies. These studies are subject to some of the same methodological flaws of the pharmacological studies, however, and the results are inconclusive.

#### A PATHOPHYSIOLOGICAL MODEL FOR IRRITABLE BOWEL SYNDROME

Patients with irritable bowel syndrome appear to have myoelectric abnormalities even in the asymptomatic state. It is possible that these abnormalities interact with the CNS to produce symptoms of irritable bowel syndrome in susceptible patients.

The enteric nervous system has been called the "third division" of the autonomic nervous system (79), structurally resembling the CNS more than the peripheral nervous system. The enteric nervous system has a myenteric-blood barrier similar to the blood-brain bar-

rier, uses glial cells for support rather than Schwann cells, and can manifest reflex activity *in vitro*, operating independently of CNS control (80). The enteric nervous system contains as many intrinsic neurons as the spinal cord (about  $10^8$ ), yet it receives only about 2,000 efferents from the CNS (80).

Many neurotransmitters and behaviorally relevant peptides commonly found in the CNS function as regulators of motility (81–84). At least 14 gastrointestinal peptides are found in the CNS (85), and although the functional activity of these neurotransmitters and peptides has not been assessed in patients with irritable bowel syndrome, one recent study suggested that cholecystokinin may induce panic-like attacks in some individuals (86).

The CNS link in the association of psychiatric disorders and irritable bowel syndrome may be the locus ceruleus (87). The locus ceruleus accounts for about 70% of all CNS noradrenergic activity, and it has been observed that higher levels of locus ceruleus activity are correlated with vigilance and attention to novel or fear-provoking stimuli, but less activation appears to be associated with behaviors such as sleep, grooming, and feeding (88). This suggests that the locus ceruleus acts as a gate controlling the signal-to-noise ratio of incoming stimuli. It appears to have substantial afferent input from the viscera (89) and receives direct innervation from the medullary nucleus solitarius (90), an area known to be a principal locus for afferent information from the gut (91).

Studies of emotional modulation of gut motility have shown that anxiety, fear, and depression result in hypomotility and that aggressive feelings such as hostility and resentment can cause hypermotility (91). Psychiatric disorders, particularly anxiety and somatization disorders, frequently involve gastrointestinal complaints. Studies have suggested that there is pathological dysregulation of the locus ceruleus in panic disorder (92, 93) and, possibly, in depression as well (94). Thus, the locus ceruleus is one possible CNS area having both afferent and efferent connections to the gut that might constitute the "missing link."

The locus ceruleus may combine cortical, limbic, and visceral sensory stimuli and then redistribute the output among the same systems in a manner that does not reach conscious awareness. Thus, internal bowel events may cause discharge of the locus ceruleus, greater anxiety, and psychophysiological gastrointestinal symptoms. The gastrointestinal symptoms may then cause peripheral activation of the locus ceruleus, resulting in greater anxiety, adding to the mental stress of the individual and further overwhelming coping mechanisms (95).

#### CLINICAL EVALUATION AND MANAGEMENT

Although not all patients with irritable bowel syndrome have psychiatric comorbidity, psychiatric referral may be beneficial in the clinical management of

many patients. The psychiatrist may be of assistance by reframing irritable bowel syndrome as a biological vulnerability that worsens with psychological distress, providing proper diagnosis and treatment of coexisting psychiatric disease and maladaptive illness behaviors, and developing a multimodal treatment plan including psychotherapeutic and pharmacological management. Psychotherapy may be useful to restore adaptive coping mechanisms, and antidepressants may be effective in patients with prominent mood symptoms. Benzodiazepines may also prove useful, but care must be taken to avoid problems with abuse and dependence in patients with somatization traits. Therapeutic goals should be restricted to symptom reduction rather than cure, since many gastrointestinal symptoms may persist after resolution of the concurrent psychiatric disorder.

The gastroenterologist may also benefit from advice on the practical management of patients with somatoform disorders, especially their high rates of use of medical services and dependent personality characteristics. The use of brief, regularly scheduled visits may help to reassure the patient that his or her symptoms are being taken seriously and may reduce symptom amplification (96).

In the psychiatric evaluation of these patients, one should pay particular attention to illness behaviors in the family of origin. Personal and family histories of chest pain, headache, low back pain, somatoform disorders, disability syndromes, and other medical conditions known to be associated with mood and anxiety disorders should be considered and noted in patients with irritable bowel syndrome.

Patients with irritable bowel syndrome manifest many noncolonic and systematic symptoms that are difficult to incorporate into a pathophysiological model of irritable bowel syndrome. Perhaps the recognition and proper treatment of coexisting psychiatric disorders and maladaptive illness behaviors will assist in the accurate elucidation of physiological features of irritable bowel syndrome.

## REFERENCES

1. Ferguson A, Sircus W, Eastwood MA: Frequency of "functional" gastrointestinal disorders. *Lancet* 1977; 2:613-614
2. Fielding JF: A year in out-patients with the irritable bowel syndrome. *Ir J Med Sci* 1977; 146:162-166
3. Liss JL, Alpers D, Woodruff RA: The irritable colon syndrome and psychiatric illness. *Dis Nerv Syst* 1973; 34:151-157
4. Young SJ, Alpers DH, Norland CC, et al: Psychiatric illness and the irritable bowel syndrome. *Gastroenterology* 1976; 70:162-166
5. Fava GA, Pavan L: Large bowel disorders, II: psychopathology and alexithymia. *Psychother Psychosom* 1976; 27:100-105
6. Latimer P, Sarna S, Campbell D, et al: Colonic motor and myoelectric activity: a comparative study of normal subjects, psychoneurotic patients and patients with irritable bowel syndrome. *Gastroenterology* 1981; 80:893-901
7. Wender PH, Kalm M: Prevalence of attention deficit disorder, residual type, and other psychiatric disorders in patients with irritable colon syndrome. *Am J Psychiatry* 1983; 140:1579-1582
8. Ford MJ, Miller PM, Eastwood J, et al: Life events, psychiatric illness and the irritable bowel syndrome. *Gut* 1987; 28:160-165
9. Latimer P: Irritable bowel syndrome. *Psychosomatics* 1983; 24: 205-218
10. Langeluddecke PM: Psychological aspects of irritable bowel syndrome. *Aust NZ J Psychiatry* 1985; 19:218-226
11. Clouse RE, Alpers DH: The relationship of psychiatric disorder to gastrointestinal illness. *Annu Rev Med* 1986; 37:283-295
12. Ford MJ: Invited review: the irritable bowel syndrome. *J Psychosom Res* 1986; 30:399-410
13. Almy TP, Rothstein RI: Irritable bowel syndrome: classification and pathogenesis. *Annu Rev Med* 1987; 38:257-265
14. Rubinow DR, Roy-Byrne PP: Premenstrual syndromes: an overview from a methodologic perspective. *Am J Psychiatry* 1984; 141:163-172
15. Drossman DA, Sandler RS, McKee DC, et al: Bowel patterns among subjects not seeking health care. *Gastroenterology* 1982; 83:529-534
16. Manning AP, Thompson WG, Heaton KW, et al: Towards a positive diagnosis of the irritable bowel. *Br Med J* 1978; 2:653-654
17. Thompson WG, Heaton KW: Functional bowel disorders in apparently healthy people. *Gastroenterology* 1980; 79:283-288
18. Whitehead WE, Schuster MM: *Gastrointestinal Disorders: Behavioral and Physiological Basis for Treatment*. Orlando, Fla, Academic Press, 1985
19. Whitehead WE, Bosmajian L, Zonderman AB, et al: Symptoms of psychologic distress associated with irritable bowel syndrome. *Gastroenterology* 1988; 95:709-714
20. Clouse RE, Lustman PJ: Psychiatric illness and contraction abnormalities of the esophagus. *N Engl J Med* 1983; 309:1337-1342
21. Sjodin I, Svedlund J: Psychological aspects of non-ulcer dyspepsia: a psychosomatic view focusing on a comparison between the irritable bowel syndrome and peptic ulcer disease. *Scand J Gastroenterol Suppl* 1985; 109:51-58
22. Talley NJ, Fung LH, Gilligan IJ, et al: Association of anxiety, neuroticism and depression with dyspepsia of unknown cause. *Gastroenterology* 1986; 90:886-892
23. Watson WC, Sullivan SN, Corke M, et al: Globus and headache: common symptoms of the irritable bowel syndrome. *Can Med Assoc J* 1978; 118:387-388
24. Sandler RS, Drossman DA, Nathan HP, et al: Symptom complaints and health care in subjects with bowel dysfunction. *Gastroenterology* 1984; 87:314-318
25. Svedlund J, Sjodin I, Dotevall G: Upper gastrointestinal and mental symptoms in the irritable bowel syndrome. *Scand J Gastroenterol* 1985; 20:595-601
26. Whorwell PJ, McCallum M, Creed FH, et al: Non-colonic features of the irritable bowel syndrome. *Gut* 1986; 27:37-40
27. Stone RT, Barbero GJ: Recurrent abdominal pain in children. *Pediatrics* 1970; 45:732-738
28. Oster J: Recurrent abdominal pain, headache and limb pains in children and adolescents. *Pediatrics* 1972; 50:429-436
29. Lowman BC, Drossman DA, Cramer EM, et al: Recollection of childhood events in adults with irritable bowel syndrome. *J Clin Gastroenterol* 1987; 9:324-330
30. Thompson WG: The irritable bowel. *Gut* 1984; 25:305-320
31. Welch GW, Hillman LC, Pomare EW: Psychoneurotic symptomatology in the irritable bowel syndrome: a study of reporters and nonreporters. *Br Med J* 1985; 291:1382-1384
32. Myers JK, Weissman MM, Tischler GL, et al: Six-month prevalence of psychiatric disorders in three communities: 1980 to 1982. *Arch Gen Psychiatry* 1984; 41:959-967
33. Uhde TW, Boulenger J-P, Roy-Byrne PP, et al: Longitudinal course of panic disorder: clinical and biological considerations. *Prog Neuropsychopharmacol Biol Psychiatry* 1985; 9:39-51
34. Weissman MM, Merikangas KR: The epidemiology of anxiety and panic disorders: an update. *J Clin Psychiatry* 1986; 47(June suppl):11-17
35. Weissman MM, Klerman GL: Sex differences in the epidemiology of depression. *Arch Gen Psychiatry* 1977; 34:98-111



36. Apley J, Hale B: Children with recurrent abdominal pain: how do they grow up? *Br Med J* 1973; 3:7-9
37. Waller SL, Misiewicz JJ: Prognosis in the irritable bowel syndrome: a prospective study. *Lancet* 1969; 2:754-756
38. Snape WJ, Carlson GM, Cohen S: Colonic myoelectric activity in the irritable bowel syndrome. *Gastroenterology* 1976; 70: 326-330
39. Snape WJ, Carlson GM, Matarazzo SA, et al: Evidence that abnormal myoelectric activity produces colonic motor dysfunction in the irritable bowel syndrome. *Gastroenterology* 1977; 72:383-387
40. Sullivan MA, Cohen S, Snape WJ: Colonic myoelectrical activity in irritable bowel syndrome. *N Engl J Med* 1978; 298:878-883
41. Taylor I, Hammond P, Basu P: Is there a myoelectrical abnormality in the irritable colon syndrome? *Gut* 1978; 19:391-395
42. Kline J, Hayek M, Hodges V, et al: Myoelectric activity in children with the recurrent abdominal pain syndrome (RAP) (abstract). *Gastroenterology* 1982; 82:1101
43. Taylor I, Darby C, Hammond P: Comparison of rectosigmoid myoelectrical activity in the irritable colon syndrome during relapses and remissions. *Gut* 1978; 19:923-929
44. Whitehead WE, Engel BT, Schuster MM: Irritable bowel syndrome: physiological differences between diarrhea-predominant and constipation-predominant patients. *Dig Dis Sci* 1980; 25: 404-413
45. Harvey RF, Read AE: Effect of cholecystokinin on colonic motility and symptoms in patients with the irritable bowel syndrome. *Lancet* 1973; 1:1-3
46. Corbett CL, Read TS, Read NW, et al: Electrochemical detector for breath hydrogen determination: measurement of small bowel transit time in normal subjects and patients with the irritable bowel syndrome. *Gut* 1981; 22:836-840
47. Kumar D, Wingate D: The irritable bowel syndrome: a paroxysmal motor disorder. *Lancet* 1985; 2:973-977
48. Ritchie J: Pain from distention of the pelvic colon by inflating a balloon in the irritable colon syndrome. *Gut* 1973; 14:125-132
49. Swabrick ET, Hegarty JE, Bat L, et al: Site of pain from the irritable bowel. *Lancet* 1980; 2:443-446
50. Cook IJ, Van Eeden A, Collins SM: Patients with irritable bowel syndrome have greater pain tolerance than normal subjects. *Gastroenterology* 1987; 93:727-733
51. Moriarty KJ, Dawson AM: Functional abdominal pain: further evidence that whole gut is affected. *Br Med J* 1982; 284:1670-1672
52. Breier A, Charney DS, Heninger GR: Major depression in patients with agoraphobia and panic disorder. *Arch Gen Psychiatry* 1984; 41:1129-1135
53. Boyd JH, Burke JD, Gruenberg E, et al: Exclusion criteria of DSM-III. *Arch Gen Psychiatry* 1984; 41:983-989
54. Helzer JE, Stillings WA, Chammas S, et al: A controlled study of the association between ulcerative colitis and psychiatric diagnosis. *Dig Dis Sci* 1982; 27:513-518
55. Helzer JE, Chammas S, Norland C, et al: A study of the association between Crohn's disease and psychiatric illness. *Gastroenterology* 1984; 86:324-330
56. Lolas F, Heerlein A: Content category analysis of affective expression in irritable bowel, duodenal ulcer and anxiety disorder patients. *Psychopathology* 1986; 19:309-316
57. Tarter RE, Switala J, Carra J, et al: Inflammatory bowel disease: psychiatric status of patients before and after disease onset. *Int J Psychiatry Med* 1987; 17:173-181
58. Whitehead WE, Winger C, Fedaravicius AS, et al: Learned illness behavior in patients with irritable bowel syndrome and peptic ulcer. *Dig Dis Sci* 1982; 27:202-208
59. Latimer PR: Irritable bowel syndrome: a behavioral model. *Behav Res Ther* 1981; 19:475-483
60. Drossman DA, McKee DC, Sandler RS, et al: Psychosocial factors in the irritable bowel syndrome. *Gastroenterology* 1988; 95:701-708
61. Robinson JO, Granfield AJ: The frequent consulter in primary medical care. *J Psychosom Res* 1986; 30:589-600
62. Tyrer P: Neurosis divisible. *Lancet* 1985; 1:685-688
63. Sullivan M, Katon WJ, Dobie R, et al: Disabling tinnitus: association with affective disorder. *Gen Hosp Psychiatry* 1988; 10:285-291
64. Klein KB: Controlled treatment trials in the irritable bowel syndrome: a critique. *Gastroenterology* 1988; 95:232-241
65. Heefner JD, Wilder RM, Wilson JD: Irritable colon and depression. *Psychosomatics* 1978; 19:540-547
66. Greenbaum DS: Preliminary report on antidepressant treatment of irritable bowel syndrome: comments on comparison with anxiolytic therapy. *Psychopharmacol Bull* 1984; 20:622-628
67. Myren J, Groth MH, Larssen SE, et al: The effects of trimipramine in patients with the irritable bowel syndrome. *Scand J Gastroenterol* 1982; 17:871-875
68. Myren J, Lovland E, Larssen SG, et al: A double-blind study of the effect of trimipramine in patients with the irritable bowel syndrome. *Scand J Gastroenterol* 1984; 19:835-843
69. Lancaster-Smith MJ, Prout BJ, Pinto T, et al: Influence of drug treatment on the irritable bowel syndrome and its interaction with psychoneurotic morbidity. *Acta Psychiatr Scand* 1982; 66: 33-41
70. Steinhart MJ, Wong PY, Zarr ML: Therapeutic usefulness of amitriptyline in spastic colon syndrome. *Int J Psychiatry Med* 1982; 11:45-57
71. Baume P, Cuthbert J: The effect of medazepam in relieving symptoms of functional gastrointestinal disorders. *Aust NZ J Med* 1973; 3:457-460
72. Ritchie JA, Truelove SC: Treatment of irritable bowel syndrome with lorazepam, hyoscine butylbromide, and ispaghula husk. *Br Med J* 1979; 1:376-378
73. Ritchie JA, Truelove SC: Comparison of various treatments for irritable bowel syndrome. *Br Med J* 1980; 281:1317-1319
74. Lydiard RB, Laraia MT, Howell EF, et al: Can panic disorder present as irritable bowel syndrome? *J Clin Psychiatry* 1986; 47:470-473
75. Schonecke O, Schuffel W: Evaluation of combined pharmacological and psychotherapeutic treatment in patients with functional abdominal disorders. *Psychother Psychosom* 1975; 26: 86-92
76. Wise TN, Cooper JN, Ahmed S: The efficacy of group therapy for patients with irritable bowel syndrome. *Psychosomatics* 1982; 23:465-469
77. Svedlund J, Sjodin I, Ottosson JO: Controlled study of psychotherapy in irritable bowel syndrome. *Lancet* 1983; 2:589-591
78. Whorwell PJ, Prior A, Faragher EB: Controlled trial of hypnotherapy in the treatment of severe refractory irritable bowel syndrome. *Lancet* 1984; 1:1232-1233
79. Langley JN: The Autonomic Nervous System, part 1. Cambridge, W Heffer & Sons, 1981
80. Gershon MD, Payette RF, Rothman TP: Development of the enteric nervous system. *Fed Proc* 1983; 42:1620-1625
81. Wood JD: Enteric neurophysiology. *Am J Physiol* 1984; 247: G585-G597
82. Stacher G, Steinringer H, Schmeier G: Stimulatory effects of the synthetic enkephalin analogue FK 33-824 on colonic motor activity antagonized by naloxone. *Hepato-Gastroenterology* 1981; 28:110-115
83. Lanfranchi GA, Bazzocchi G, Fois F, et al: Effect of domperidone and dopamine on colonic motor activity in patients with the irritable bowel syndrome. *Eur J Clin Pharmacol* 1985; 29:307-310
84. Krantis A, Harding RK: GABA-related action in isolated in vitro preparations of the rat small intestine. *Eur J Pharmacol* 1987; 141:291-298
85. Krieger DT: Brain peptides: what, where, why? *Science* 1983; 222:975-985
86. de Montigny C: Cholecystokinin tetrapeptide induces panic-like attacks in healthy volunteers. *Arch Gen Psychiatry* 1989; 46: 511-517
87. Svensson THE: Peripheral, autonomic regulation of locus coeruleus noradrenergic neurons in brain: putative implications for psychiatry and psychopharmacology. *Psychopharmacology* 1987; 92:1-7
88. Foote SL, Bloom FE, Aston-Jones C: Nucleus locus coeruleus:

- new evidence of anatomical and physiological specificity. *Physiol Rev* 1983; 63:844-914
89. Elam M, Svensson THE, Thoren P: Locus coeruleus neurons and sympathetic nerves: activation by visceral afferents. *Brain Res* 1986; 375:117-125
  90. Gorman JM, Liebowitz MR, Fyer AJ, et al: A neuroanatomical hypothesis for panic disorder. *Am J Psychiatry* 1989; 146:148-161
  91. Gillis RA, Quest JA, Pagani FD, et al: Control centers in the central nervous system for regulating gastrointestinal motility, in *Handbook of Physiology*. New York, Oxford University Press (in press)
  92. Charney DS, Heninger GR, Breier A: Noradrenergic function in panic anxiety. *Arch Gen Psychiatry* 1984; 41:751-763
  93. Charney DS, Heninger GR: Abnormal regulation of noradrenergic function in panic disorders. *Arch Gen Psychiatry* 1986; 43:1042-1054
  94. Siever LJ, Uhde TW, Jimerson DC, et al: Differential inhibitory noradrenergic responses to clonidine in 25 depressed patients and 25 normal control subjects. *Am J Psychiatry* 1984; 141:733-741
  95. Katon WJ, Roy-Byrne PP: Panic disorder in the medically ill. *J Clin Psychiatry* 1989; 50:299-302
  96. Smith GR, Monson RA, Ray DC: Psychiatric consultation in somatization disorder. *N Engl J Med* 1986; 314:1407-1413

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## Inverse Relationship Between Defensiveness and Lifetime Prevalence of Psychiatric Disorder

Richard D. Lane, M.D., Kathleen R. Merikangas, Ph.D., Gary E. Schwartz, Ph.D.,  
Suzanne S. Huang, M.P.H., and Brigitte A. Prusoff, Ph.D.

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*Defensiveness (the tendency not to report unfavorable information about oneself), as measured by the Marlowe-Crowne Social Desirability Scale, has been shown to be inversely correlated with self-reported symptoms. In this family study of depression, direct interviews with 380 subjects combined with relatives' reports revealed a similar inverse relationship between defensiveness and lifetime prevalence of any psychiatric disorder, especially when diagnostic status was most certain and among those at greater risk for psychopathology. The authors conclude that the Marlowe-Crowne scale measures a factor or trait associated with the relative absence of psychiatric disorder, not the underreporting or denial of disorder.*

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Although other sources of information are routinely used to assign diagnoses for clinical or research purposes, patients' self-reports play an important role in determining the outcome of diagnostic assessments. This is particularly true when structured interviews such as the Schedule for Affective Disorders and Schizophrenia (SADS) (1) and the National Institute of Mental Health Diagnostic Interview Schedule (DIS) (2) serve as the basis for research diagnoses. However, a long tradition in the field of psychological (3) and psychiatric (4-7) assessment has demonstrated that self-reports of symptoms may be less accurate than clinical assessments. Previous studies (8-10), including three community surveys of mental health (11-13), have found an inverse association between defensiveness, as measured by the Marlowe-Crowne Social Desirability Scale (14), and scores on self-report symptom inventories. These data raise the question of whether diagnostic assessments derived solely from self-reported symptoms may be less valid among defensive subjects when they are asked to report on negative attributes.

The Marlowe-Crowne scale was developed in 1960 to measure the tendency to present oneself in an especially positive light. It was essentially intended as a measure of "other-deception": "the truth" is known to the subject but is not presented in order to win social approval. More recently, the Marlowe-Crowne scale has been thought to measure self-deception as well—the subject, unconsciously protecting his or her vulnerable self-esteem, is unaware of unpleasant emotional realities and therefore does not report them (15-19). According to the original design of the scale, self-reports are thought to be inaccurate because they are knowingly biased by the subject in a favorable direction. Such distortions could lead to underestimates of the prevalence of psychiatric disorder. According to the later interpretation of the scale, however, self-re-



ports are an accurate reflection of what the subject knows and do not involve intentional distortion. To the extent that psychiatric disorders are defined by the symptoms that people experience, lower rates of disorder among defensive subjects would thus be accurate.

Distinguishing between these two alternatives in evaluating the accuracy of self-reported psychopathology has been difficult because previous research has generally not provided external validation of self-reported symptoms. However, two studies (13, 20) have demonstrated that when correlations between self-reported symptoms and an objective assessment of symptoms were corrected for "social desirability," the correlations did not increase, as would be expected if the Marlowe-Crowne scale were measuring other-deception during self-report. Rather, such findings suggest that the self-reported symptoms were accurate and that the measure of social desirability reflects a substantive personality variable which is actually associated with fewer symptoms, consistent with the self-deception interpretation of the Marlowe-Crowne scale. Based on these findings, therefore, one would predict that lifetime prevalence of psychiatric disorder diagnosed according to modern methods is truly lower among individuals who score higher on the Marlowe-Crowne scale.

Although previous studies have found a direct association between Marlowe-Crowne scale scores and age (11, 12) and sex (21), to our knowledge these associations have not been confirmed in a study using the full 33-item version of the Marlowe-Crowne scale in adults of varying ages. Furthermore, the community surveys that assessed the relationship between self-reported symptoms and Marlowe-Crowne scale scores used symptom inventories that are not currently in use in modern studies in psychiatric epidemiology. In the present study, the association between scores on the Marlowe-Crowne scale and the Symptom Checklist-90 (SCL-90) (22), which has demonstrated reliability and validity and assesses a variety of psychopathological symptoms (23, 24), was examined for the purposes of replicating previous research by using newer methods and demonstrating the applicability of previous research to our sample.

Based on the above considerations, we predicted 1) an inverse correlation between scores on the Marlowe-Crowne scale and the SCL-90 and 2) an inverse association between scores on the Marlowe-Crowne scale and lifetime prevalence of research diagnostic criteria (RDC)-defined psychiatric disorders (25) according to the SADS-L (26, 27). Furthermore, we also wished to determine whether these relationships were altered by controlling for age and sex and whether the self-deception or other-deception interpretation of the Marlowe-Crowne scale was more valid.

## METHOD

Comprehensive clinical assessments of depressed and normal probands and their adult first-degree rel-

atives (parents, siblings, and children) were made through direct diagnostic interviews using a modification of the lifetime version of the Schedule for Affective Disorders and Schizophrenia (SADS-L) RDC (25-27). A retrospective cohort design was used in which the lifetime history of any psychiatric diagnosis was the major outcome of interest.

The subjects for this study came from the family study of depression of Weissman et al. (28). All of the probands were white, and the depressed and normal groups were matched for sex and age. The depressed probands met RDC criteria with slight modifications for major nonbipolar depression, had all received treatment for depression, and were generally not receiving treatment at the time of entry into the study. The normal probands were drawn from a population sample that had been followed longitudinally between 1967 and 1976, reinterviewed on at least three occasions during that period, and had given no evidence of psychiatric disorder or treatment, either by history or at interview.

A diagnostic assessment was made of every living first-degree relative and spouse who was residing in the United States. Relatives were interviewed with a modified SADS-L interview (29). In addition, family history data were obtained from multiple informants and from medical records on all other first-degree relatives, living or dead (30). A total of 40% of the relatives were directly interviewed.

Diagnoses were made according to RDC from each direct interview. Family history reports and the results of the direct interview plus treatment records when relevant were then blindly reviewed separately by two clinicians, who then assigned a "best estimate diagnosis" based on all of the information (31, 32).

Two self-report measures were used in this study. The Marlowe-Crowne scale (14) is a 33-item true-false questionnaire derived in part from the F, L, K, and manifest anxiety subscales of the MMPI and is designed so that neither response on any item is suggestive of psychopathology. Fifteen items keyed false (the denial subscale) are probable but socially desirable (e.g., "I am sometimes irritated by people who ask favors of me"), and 18 items keyed true (the attribution subscale) are improbable but socially desirable (e.g., "No matter who I'm talking to, I am always a good listener"). The more items endorsed as keyed, the higher the score on defensiveness. Ninety-eight probands, 227 relatives, and 55 spouses completed the Marlowe-Crowne scale.

The SCL-90 (22) is a 90-item list of words or phrases describing psychopathological symptoms that are each rated on a 5-point scale of severity. The total score is the sum of the values endorsed for each item. Further details of the methodology are reported elsewhere (28).

## RESULTS

The distribution of Marlowe-Crowne scale scores by age and sex is shown in table 1. In general, there was

**TABLE 1. Age, Sex, and Marlowe-Crowne Social Desirability Scale Scores of Depressed and Normal Probands (N=98) and Their Relatives (N=227) and Spouses (N=55)<sup>a</sup>**

Age and Sex	N	Mean Marlowe-Crowne Score
Age group (years)		
0-19	13	17.03
20-29	76	16.84
30-39	64	18.31
40-49	75	20.17
50-59	78	21.44
60 and older	74	23.45
Sex		
Male	169	18.58
Female	211	21.03

<sup>a</sup>Significant difference in scores by age (adjusted for sex) ( $F=34.57$ ,  $df=1, 377$ ,  $p<0.0001$ ). Significant difference in scores by sex (adjusted for age) ( $F=17.95$ ,  $df=1, 377$ ,  $p<0.0001$ ). Significant difference in scores for the combined effects of age and sex, excluding any interactions between age and sex ( $F=26.26$ ,  $df=2, 377$ ,  $p<0.0001$ ).

a linear increase in total Marlowe-Crowne scale score with increasing age. Consistent with other studies, women scored significantly higher on total Marlowe-Crowne scale than men. The interaction between sex and age was not significant.

The correlations between total SCL-90 score and Marlowe-Crowne scale total score ( $r=-0.3469$ ) and subscale scores (denial subscale,  $r=-0.4197$ ; attribution subscale,  $r=-0.1932$ ) were all significant ( $p<0.0001$ ;  $df=379$ ) and in the predicted direction. These correlations remained significant even when the effects of sex and age were controlled. The magnitude of the significance values is in part a function of the large sample size ( $N=380$ ).

Table 2 shows the total Marlowe-Crowne scale scores for the entire sample and for various subgroups classified according to presence or absence of any lifetime psychiatric disorder by the interviewer's RDC ratings. Consistent results in the predicted direction were observed for all groups.

The results for probands and their relatives were highly significant. However, these results were no longer significant when age and sex were controlled. Table 2 also shows that among relatives of depressed probands, those who had a past history of psychiatric disorder had significantly lower Marlowe-Crowne scale scores than those who did not, but among relatives of normal probands, this same trend was not statistically significant. These findings suggest that the association between defensiveness and psychiatric disorder is greater among relatives at higher risk for psychiatric disorder.

We then determined whether the best estimate method yielded results different from those with interview ratings. Since any potential probands were excluded whose interview and best estimate diagnoses disagreed, the scores for probands diagnosed according to the two methods were identical. For all relatives, the best estimate method identified 45 individuals with

**TABLE 2. Lifetime History of RDC Psychiatric Disorder and Marlowe-Crowne Social Desirability Scale Scores of Depressed and Normal Probands (N=98) and Their Relatives (N=227) and Spouses (N=55)**

Group	N	Mean Marlowe-Crowne Score	t	df	p
Entire sample			5.22	378	0.0001
Any disorder	183	18.26			
No disorder	197	21.51			
Probands			4.65	96	0.0001
Any disorder	62	17.64			
No disorder	36	22.78			
All relatives			3.04	225	0.003
Any disorder	97	18.48			
No disorder	130	21.07			
Relatives of normal probands			1.69	76	0.10
Any disorder	26	19.38			
No disorder	52	21.74			
Relatives of depressed probands			2.28	147	0.02
Any disorder	71	18.15			
No disorder	78	20.62			

a disorder that was not detected on interview (interview diagnoses, when present, were never nullified by additional information). Nevertheless, the difference in total mean  $\pm$  SD Marlowe-Crowne scale score between those with ( $19.21 \pm 6.70$ ) and those without ( $21.07 \pm 5.97$ ) disorder remained significant ( $t=2.12$ ,  $df=226$ ,  $p<0.03$ ). Thus, the inclusion of the ancillary information from family history reports did not change the association between Marlowe-Crowne scale score and diagnoses. This suggests that denial of symptoms is not a likely explanation for the inverse association between Marlowe-Crowne scale score and diagnostic status.

To further examine whether the Marlowe-Crowne scale was detecting denial, we identified groups of "deniers" and "nondeniers" and compared their Marlowe-Crowne scale scores. Subjects who denied the symptom probes in the direct SADS-L interview for the sections on depression, anxiety, and alcoholism and/or drug abuse but ultimately received that diagnosis after reports from relatives indicated the presence of that syndrome were classified as deniers. Those who both endorsed the SADS-L symptom probe at interview and received that diagnosis after ancillary information was incorporated into the diagnostic estimate were classified as nondeniers.

Table 3 presents the results of the comparison between Marlowe-Crowne scale scores of the deniers and nondeniers. No significant differences emerged for any of the diagnostic categories, although deniers of drug abuse showed a trend toward greater Marlowe-Crowne scale scores than did nondeniers. Therefore, although the number of subjects was small, the Marlowe-Crowne scale did not discriminate between those subjects who denied and those who did not deny symp-

**TABLE 3. Scores on the Marlowe-Crowne Social Desirability Scale of Individuals Classified as True Positive (Nondeni-ers) or False Negative (Deniers) for Selected Disorders**

Disorder	N	Marlowe-Crowne Score		F <sup>a</sup>	df	p
		Mean	SD			
Drug abuse				3.40	1, 19	0.09
True positive	19	15.5	7.4			
False negative	4	21.0	8.1			
Alcoholism				6.99	1, 52	n.s.
True positive	54	14.3	7.2			
False negative	2	16.0	5.6			
Generalized anxiety disorder				0.54	1, 95	n.s.
True positive	86	14.9	7.0			
False negative	13	14.3	8.2			
Major depression				1.61	1, 110	n.s.
True positive	105	14.7	7.1			
False negative	9	8.1	4.6			

<sup>a</sup>Linear model controlling for sex and age.

toms but actually manifested such symptoms according to close relatives' observations.

## DISCUSSION

The primary finding in this study is that greater defensiveness is associated with lower lifetime prevalence of psychiatric disorder. We also replicated the observation of previous community surveys that greater defensiveness is associated with lower scores on inventories of self-reported symptoms. The latter finding remained significant when age and sex were controlled but the former did not, reflecting differences in the number of subjects, the statistics used, and the size of the effect. Nevertheless, the association between defensiveness and lifetime prevalence of psychiatric disorder remains valid. Based on previous studies using the Marlowe-Crowne scale, this result means either that defensiveness protects against psychiatric disorder or that defensiveness leads to the underreporting of disorder.

There are several pieces of evidence which suggest that, rather than reflecting underreporting of disorder, the Marlowe-Crowne scale detects a trait which protects against psychiatric disorder. 1) The inverse relationship between Marlowe-Crowne scale scores and psychiatric diagnoses persisted when ancillary information was incorporated into diagnostic assignment. 2) The proband group, which was meticulously screened on numerous occasions so that the likelihood of misdiagnosis in this group was much lower than it was among relatives, showed a much stronger inverse association between Marlowe-Crowne scale score and psychiatric disorder than did the relatives. 3) The relatives of depressed probands, who were at greater risk for disorder than were relatives of normal probands, exhibited a stronger association between defensiveness

and diagnosis than did those at lesser risk. 4) Marlowe-Crowne scale scores of individuals falsely classified as negative on interview were not consistently higher than those of individuals accurately classified as positive on interview, as would be expected if Marlowe-Crowne scale measured denial.

The conclusion that denial or underreporting of illness was not associated with defensiveness rules out the other-deception interpretation of the Marlowe-Crowne scale and suggests that the association with psychiatric diagnosis is with self-deception. This is consistent with Sackeim and Gur's study (33), which showed that self-deception rather than other-deception accounts for the negative correlation between scores on the Marlowe-Crowne scale and scores on symptom inventories. Based on these and other findings, Sackeim (34) suggested that impairments in the capacity to deceive oneself about unpleasant realities, as reflected by low scores on the Marlowe-Crowne scale, may be associated with a greater propensity for psychopathology such as depression. This view is supported by data showing that the perceptions of depressed people about the objective world are accurate but that the inferences and interpretations about these events are negatively biased compared with those of nondepressed individuals (35). In contrast, people who score high on the Marlowe-Crowne scale are invested in maintaining an image of themselves as not prone to negative affects such as anxiety and depression (36). To do so, they selectively attend to the positive and avoid the negative aspects of stimuli so that for them the negative tends not to exist. Accordingly, a high score on the Marlowe-Crowne scale appears to reflect an unconsciously motivated method of self-regulation that promotes emotional stability and may protect against disorder but does not compromise the accuracy of symptom self-report. It is also possible, however, that the capacity for self-deception decreases as a result of an episode of psychiatric disorder. Although research to date has not addressed this question, a clear answer to it could be obtained by prospectively studying individuals with no past history of but at high risk for psychiatric disorder. This alternative hypothesis would predict that the Marlowe-Crowne scale scores of those who have become ill after a specified follow-up interval will decrease from baseline while the Marlowe-Crowne scale scores of those who have not become ill will not decrease.

The conclusion that defensiveness appears to protect against disorder contrasts with the psychodynamic view that mental health involves attending to rather than avoiding one's affects and impulses. Other studies involving the Marlowe-Crowne scale suggest that in fact the repressive style of self-regulation at times is associated with physiological and/or behavioral dysfunction. For example, a repressive coping style as measured by the Marlowe-Crowne scale is associated with higher rates and greater severity of certain systemic medical disorders (37, 38). Another series of studies (39) found that the majority of individuals imprisoned



for sudden, extremely violent acts were repressive rather than undercontrolled. Thus, the protection from psychiatric disorder afforded by defensiveness may be associated with tradeoffs in other domains of health and may impose limits on the flexibility of one's adaptive capacities.

One of the paradoxical findings in recent epidemiologic studies is that lifetime prevalence of depression decreases with increasing age (40). Our findings of a positive correlation between Marlowe-Crowne scale scores and age and an inverse relationship between Marlowe-Crowne scale scores and psychiatric disorder are certainly consistent with this idea. Although several explanations were given for how this finding could be artifactual, one that corresponds to the positive correlation between Marlowe-Crowne scale score and age is that "younger and better educated individuals have been socialized to monitor their inner emotional states and to give greater value to psychological mindedness than have individuals growing up in different historical eras" (40, p. 692). This explanation assumes that the tendency not to monitor inner emotional states leads to deficits in the encoding of past episodes of depression and/or their retrieval from memory, i.e., that past episodes did occur but were not reported. However, our data suggest that the tendency not to monitor inner emotional states is instead protective against psychiatric disorder and that the higher rates of depression in younger cohorts are real.

Another consistent finding in recent epidemiologic studies is that for many disorders women have higher rates of psychopathology than men (41, 42). Since women tend to report more symptoms than men (43), it has been suggested that these apparent sex differences are due to reporting bias and do not reflect a true difference (44, 45). Our data show that across all ages, women scored higher on the Marlowe-Crowne scale than men. In the light of our other findings, however, we can conclude that this sex difference in Marlowe-Crowne scale scores does not reflect a tendency of women to deny symptoms. In fact, data from several studies (46, 47) converge in concluding that women are much less likely to deny symptoms than men.

In conclusion, this study demonstrates that an inverse association exists between defensiveness and lifetime prevalence of psychiatric disorder. Since this association was still observed when external information was applied, since it was strongest among those whose diagnostic status was most certain, since a greater effect of defensiveness was observed in the group at greater risk for psychopathology, and since known deniers did not have higher Marlowe-Crowne scale scores than nondeniers, we conclude that defensiveness protects against psychopathology.

Given the relative weakness of the association with lifetime prevalence of psychiatric disorder, however, the replicability of these findings must be examined. Future studies that examine the relationship between Marlowe-Crowne scale scores and other external validation criteria are indicated. Whether this association

applies to all psychopathology or only to certain categories of disorder also needs to be examined. The hypothesis that the Marlowe-Crowne scale assesses a personality trait that is associated with the absence of psychiatric disorder should also be further investigated. Possible strategies include 1) using other similar measures such as the Self-Deception Questionnaire (33, 48), which assesses defensiveness against psychiatric conditions, 2) determining whether groups at greater risk for psychopathology show a greater influence of defensiveness on rates of disorder than do those at lesser risk, and 3) assessing the relationship between Marlowe-Crowne scale and more enduring psychopathology, such as the conditions specified in axis II of *DSM-III-R*. Additionally, longitudinal assessment of the relationship between defensiveness and psychopathology is indicated.

#### REFERENCES

1. Spitzer RL, Endicott J: Schedule for Affective Disorders and Schizophrenia (SADS), 3rd ed. New York, New York State Psychiatric Institute, Biometrics Research, 1977
2. Robins LN, Helzer JE, Croughan J, et al: The National Institute of Mental Health Diagnostic Interview Schedule: its history, characteristics, and validity. *Arch Gen Psychiatry* 1981; 38:381-389
3. McKinley JC, Hathaway SR, Meehl PE: The MMPI, VI: the K scale. *J Consult Psychol* 1948; 12:20-31
4. Prusoff BA, Klerman G, Paykel ES: Concordance between clinical assessments and patients' self-report in depression. *Arch Gen Psychiatry* 1969; 26:546-552
5. Paykel ES, Prusoff BA, Klerman GL, et al: Self-report and clinical interview ratings in depression. *J Nerv Ment Dis* 1973; 156:166-182
6. Weissman MM, Sholomskas D, Pottenger M, et al: Assessing depressive symptoms in five psychiatric populations: a validation study. *Am J Epidemiol* 1977; 106:203-214
7. Boyd JH, Weissman MM, Thompson D, et al: Screening for depression in a community sample. *Arch Gen Psychiatry* 1982; 39:1195-1200
8. Rock DL: The confounding of two self-report assertion measures with the tendency to give socially desirable responses in self-description. *Consult Clin Psychol* 1981; 49:743-744
9. Linehan MM, Nielson SL: Assessment of suicide ideation and parasuicide: hopelessness and social desirability. *J Consult Clin Psychol* 1981; 49:773-775
10. Tanaka-Matsumi J, Kameoka VA: Reliabilities and concurrent validities of popular self-report measures of depression, anxiety and social desirability. *J Consult Clin Psychol* 1986; 54:328-333
11. Klassen D, Hornsra R, Anderson P: Influence of social desirability on symptom and mood reporting in a community survey. *J Consult Clin Psychol* 1975; 43:448-452
12. Gove W, Geerken M: Response bias in surveys of mental health: an empirical investigation. *AJS* 1977; 82:1289-1317
13. McCrae RR, Costa PT: Social desirability scales: more substance than style. *J Consult Clin Psychol* 1983; 51:882-888
14. Crowne D, Marlowe D: A new scale of social desirability independent of psychopathology. *J Consult Psychol* 1960; 24:1397-1403
15. Evans R: The relationship of the Marlowe-Crowne scale and its components to defensive preferences. *J Pers Assess* 1979; 43:406-410
16. Millham J, Kellogg RW: Need for approval: impression management or self-deception? *J Research in Personality* 1980; 14:445-457
17. Evans R: Clinical relevance of the Marlowe-Crowne scale: a

- review and recommendations. *J Pers Assess* 1982; 46:415-425
18. Arkin R, Lake E: Plumbing the depths of the bogus pipeline: a reprise. *J Research in Personality* 1983; 17:81-88
  19. Paulhus DL: Self-deception and impression management in test responses, in *Personality Assessment via Questionnaire*. Edited by Anglietner A, Wiggins JS. New York, Springer-Verlag, 1986
  20. Dicken C: Good impression, social desirability, and acquiescence as suppressor variables. *Educational and Psychological Measurement* 1963; 23:699-720
  21. Cosentino F, Kahn M: Further normative and comparative data on the repression-sensitization and social desirability scales. *Psychol Rep* 1967; 20:959-962
  22. Derogatis LR, Lipman RS, Covi L: SCL-90: an outpatient psychiatric scale—preliminary report. *Psychopharmacol Bull* 1973; 9:13-28
  23. Derogatis LR, Rickels K, Rock AF: The SCL-90 and the MMPI: a step in the validation of a new self-report scale. *Br J Psychiatry* 1976; 128:280-289
  24. Derogatis LR, Cleary PA: Confirmation of the dimensional structure of the SCL-90: a study in construct validation. *J Clin Psychol* 1977; 33:981-989
  25. Spitzer RL, Endicott J, Robins E: Research Diagnostic Criteria: rationale and reliability. *Arch Gen Psychiatry* 1978; 35:777-782
  26. Spitzer RL, Endicott J: *Schedule for Affective Disorders and Schizophrenia—Lifetime Version*, 3rd ed. New York, New York State Psychiatric Institute, Biometrics Research, 1979
  27. Masure E, Gershon ES: Blindness and reliability in lifetime psychiatric diagnosis. *Arch Gen Psychiatry* 1979; 36:379-384
  28. Weissman MM, Gershon ES, Kidd KK, et al: Psychiatric disorders in the relatives of probands with affective disorders: the Yale University-National Institute of Mental Health Collaborative Family Study. *Arch Gen Psychiatry* 1984; 41:13-21
  29. Meyers JK, Lindenthal JJ, Pepper MP, et al: Life events and mental status: a longitudinal study. *J Health Soc Behav* 1972; 13:398-406
  30. Thompson WD, Kidd JR, Weissman MM: A procedure for the efficient collection and processing of pedigree data suitable for genetic analysis. *J Psychiatr Res* 1979; 15:291-303
  31. Weissman MM, Myers JK, Harding PS: Psychiatric disorders in a US urban community, 1975-1976. *Am J Psychiatry* 1978; 135:459-462
  32. Leckman J, Sholomskas D, Thompson W, et al: Best estimate of lifetime psychiatric diagnosis. *Arch Gen Psychiatry* 1982; 39: 879-883
  33. Sackeim HA, Gur RC: Self-deception, other-deception and self-reported psychopathology. *J Consult Clin Psychol* 1979; 47: 213-215
  34. Sackeim HA: Self-deception, self-esteem and depression: the adaptive value of lying to oneself, in *Empirical Studies of Psychoanalytical Theories*, vol 1. Edited by Masling J. Hillsdale, NJ, Analytic Press, 1983
  35. Rehm LP: Self management and cognitive processes in depression, in *Cognitive Processes in Depression*. Edited by Alloy LB. New York, Guilford Press, 1988
  36. Weinberger DA: The construct validity of the repressive coping style, in *Repression and Dissociation: Implications for Personality Theory, Psychopathology, and Health*. Edited by Singer J. Chicago, University of Chicago Press, 1990
  37. Schwartz GE: Disregulation theory and disease: applications to the repression/cerebral disconnection/cardiovascular disorder hypothesis. *Int Rev Appl Psychol* 1983; 32:95-118
  38. Schwartz GE: Psychobiology of repression and health: a systems approach, in *Repression and Dissociation: Implications for Personality Theory, Psychopathology, and Health*. Edited by Singer J. Chicago, University of Chicago Press, 1990
  39. Megargee EL, Cook PE, Mendelsohn GA: Development and validation of an MMPI scale of assaultiveness in overcontrolled individuals. *J Abnorm Psychol* 1967; 72:519-528
  40. Klerman GL, Lavori PW, Rice J, et al: Birth-cohort trends in rates of major depressive disorder among relatives of patients with affective disorder. *Arch Gen Psychiatry* 1982; 42:689-693
  41. Weissman M, Kidd K, Prusoff B: Variability in rates of affective disorders in relatives of depressed and normal probands. *Arch Gen Psychiatry* 1982; 39:1397-1403
  42. Robins LN, Helzer JE, Weissman MM, et al: Lifetime prevalence of specific psychiatric disorder in three sites. *Arch Gen Psychiatry* 1984; 41:949-958
  43. Tousignant M, Brosseau R, Tremblay L: Sex biases in mental health scales: do women tend to report less serious symptoms and confide more than men? *Psychol Med* 1987; 17:203-215
  44. Phillips D, Segal B: Sexual status and psychiatric symptoms. *Am Sociological Rev* 1969; 34:58-72
  45. Cooperstock R: Sex differences in the use of mood-modifying drugs: an explanatory model. *J Health Soc Behav* 1971; 12: 238-244
  46. Clancy K, Gove W: Sex differences in mental health: an analysis of response bias in self-reports. *AJS* 1974; 80:205-216
  47. Briscoe M: Identification of emotional problems in postpartum women by health visitors. *Br Med J* 1986; 292:1245-1247
  48. Linden W, Paulhus DL, Dobson KS: Effects of response styles on the report of psychological and somatic distress. *J Consult Clin Psychol* 1986; 54:309-313

# Caffeine Augmentation of ECT

C. Edward Coffey, M.D., Gary S. Figiel, M.D.,  
Richard D. Weiner, M.D., Ph.D., and William B. Saunders, M.P.H.

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*In a randomized, double-blind, placebo-controlled pilot study of 40 depressed inpatients, the authors compared two techniques for maintaining seizure duration during pulse unilateral ECT: pretreatment with intravenous caffeine versus electrical stimulus intensity dosing. Both techniques effectively maintained seizure duration, but with caffeine this was accomplished without any increase in mean stimulus intensity over the course of ECT. There were no differences between the two techniques in therapeutic outcome or cognitive side effects from ECT, and caffeine pretreatment was well tolerated. The authors discuss the clinical and research implications of these findings with respect to strategies for maintaining seizure duration during ECT.*

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Work by our group (1, 2) and others (3, 4) has indicated that intravenous caffeine can lengthen seizures during ECT. These findings have raised the consideration that continued use of caffeine during ECT might obviate the need for increases in stimulus charge that are typically required over the course of therapy (5). Still, no study has examined whether caffeine pretreatment would be a safe or effective alternative to the standard clinical approach of stimulus intensity dosing in order to maintain seizure duration throughout a course of ECT. A direct comparison of these two techniques would have important clinical and research implications, since several studies (5–10) have suggested that the intensity of the ECT stimulus may be related to both the therapeutic effects and the adverse cognitive effects of the therapy.

To clarify these important issues, we conducted a randomized, double-blind, placebo-controlled investigation of two techniques for maintaining seizure du-

ration during ECT: caffeine pretreatment versus stimulus intensity dosing. This pilot study was designed to address the following questions: 1) Can caffeine pretreatment maintain seizure duration over a course of ECT in the absence of increases in stimulus intensity? and 2) How does the continued use of caffeine during ECT affect the therapeutic and adverse effects of the treatment?

## METHOD

### Subjects

The subjects were 40 inpatients with *DSM-III* major depression who had been referred for pulse unilateral nondominant ECT (see table 1). Written informed consent was obtained from each subject. Before random assignment to the two ECT treatment conditions, all subjects received an extensive neuropsychiatric evaluation performed by the ECT Service. Diagnoses were determined by the ECT Service together with the subjects' attending physicians and ward treatment teams by formal application of *DSM-III* criteria. For each subject, daily caffeine consumption for the 2 weeks before admission was estimated according to the quantities of caffeine found in drugs, chocolate bars, and different beverages (11). There were no significant differences between the two subject groups in mean age, sex, diagnosis, presence of psychosis, or pre-ECT caffeine use (see table 1).

The majority of the subjects were medically healthy, but 14 were maintained on one or more nonpsychotropic medications (11 received diuretic and/or antihypertensive medications, three received thyroid supplements, and three received antianginal medications). In general, the doses of these medications were optimized and then held constant throughout the course of the ECT treatments. Beginning with the second ECT treatment, however, three subjects (all in the group given stimulus intensity dosing) received intravenous premedication with 5 mg of the antihypertensive labetalol 5 minutes before the ECT stimulus. This medication was administered at the discretion of the attending anesthesiologist, who felt that each of these subjects had experienced unacceptably high blood pressures and pulse rates during their first ECT treatment.

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**TABLE 1. Baseline Clinical Characteristics of 40 Depressed Inpatients Given ECT With Caffeine Pretreatment or Stimulus Intensity Dosing**

Item	Caffeine Group (N=20)	Stimulus Intensity Dosing Group (N=20)
Age		
Mean	51.00	58.00
SD	13.36	18.47
Range	29–75	32–81
Sex		
Number of men	7	7
Number of women	13	13
Montgomery-Asberg Depression Rating Scale score		
Mean	36.5	39.4
SD	7.10	8.15
Carroll Self-Rating Depression Scale score		
Mean	29.3	28.8
SD	7.63	9.75
Diagnosis (DSM-III)		
Major depression with melancholia		
Number	12	15
Percent	60	75
Major depression without melancholia		
Number	1	4
Percent	5	20
Bipolar disorder, depressed with melancholia		
Number	4	1
Percent	20	5
Bipolar disorder, depressed without melancholia		
Number	2	0
Percent	10	0
Schizoaffective disorder, depressed		
Number	1	0
Percent	5	0
Psychotic symptoms present		
Number	3	3
Percent	15	15
Oral caffeine intake before ECT administration (mg/day)		
Mean	335	265
SD	210	162

### ECT Treatment Technique

All subjects were free of psychotropic medications at the time of the first ECT treatment. The duration of the pre-ECT drug-free period ranged from 1 to 14 days and depended primarily on the subject's severity of illness and the clinical treatment team's perception of the urgency to begin therapy. During the course of ECT treatments, 10 subjects (six in the caffeine group and four in the group given stimulus intensity dosing) received occasional as-needed doses of neuroleptic medications for control of severe agitation and/or post-ECT treatment nausea. An additional three subjects received as-needed doses of benzodiazepines during the course of ECT treatment for control of either marked anxiety (one patient in the caffeine group received alprazolam, and one patient in the group given

stimulus intensity dosing received triazolam) or post-ECT emergent delirium (one subject in the group given stimulus intensity dosing received diazepam).

The ECT treatment technique was similar for each subject. ECT was administered three mornings a week, on Monday, Wednesday, and Friday, in a special ECT treatment suite. Subjects received anticholinergic premedication with either 0.002 mg/lb of intramuscular glycopyrrolate (N=30) or 0.1 mg/10 kg of intravenous atropine (N=5) before ECT. Five subjects received no anticholinergic premedications due to sensitivity to the side effects of these drugs. Anesthesia was induced with 1 mg/kg of intravenous methohexital, followed by 1 mg/kg of intravenous succinylcholine, to produce subtotal neuromuscular blockade. All subjects were preoxygenated with 100% oxygen through a mask. When they were apneic, their respirations were maintained at 20–25/min with positive pressure ventilation by bag until spontaneous respirations returned. The d'Elia unilateral nondominant ECT stimulus electrode placement technique (12) was used. The pulse stimulus was administered by a Mecta SR-1 brief pulse device. For each ECT treatment, seizure duration was determined from the one-channel EEG by a Board-certified electroencephalographer (R.D.W.) who was blind to the subject's experimental status (the caffeine group versus the group given stimulus intensity dosing). The total number of ECT treatments was determined by the subject's ward treatment team, which was also blind to the subject's experimental status.

Stimulus dose measures for the first ECT treatment were adjusted for age: subjects 60 years old or older received 168 millicoulombs and those younger than 60 years received 120 millicoulombs (millicoulombs, a measure of charge, provides a composite index of stimulus intensity) (13). The single exception was a 37-year-old woman in the group given stimulus intensity dosing who was known from previous ECT treatment courses to require a lower stimulus dose—her initial stimulus charge was 60 millicoulombs. For the three patients with seizure durations at the first ECT treatment of less than 30 seconds and the 17 patients with seizure durations greater than 100 seconds, stimulus charge settings were increased or decreased by 30%, respectively, at the second ECT treatment.

### Caffeine Versus Stimulus Intensity Dosing Protocol

Beginning with the second ECT treatment, subjects were randomly assigned to receive either caffeine and sodium benzoate or placebo (2 cc of normal saline in the group given stimulus intensity dosing) for the remainder of their course of therapy. Both subjects and their clinical treatment teams were kept blind to this assignment. This protocol was not implemented until the second ECT treatment to determine independently of the effects of caffeine the need for any modifications in the ECT technique used during the first treatment (adjustments in doses of anesthesia or muscle relaxant

and the need for antihypertensive medication during ECT, for example).

A starting dose of 242 mg of caffeine (one 2-cc vial) was used. The caffeine was administered by means of intravenous push over 30 seconds after baseline vital signs had been obtained. Vital signs were obtained again 2 minutes after the caffeine infusion was completed; during this interval, subjects were observed for any signs or symptoms of anxiety. The anesthesia, muscle relaxant, and oxygen were then administered as described above. The delivery of the stimulus was timed to occur 5 minutes after completion of the caffeine infusion. The procedure for administering placebo to the group given stimulus intensity dosing was identical to that for the group given caffeine.

Beginning with the second ECT treatment, the technique for maintaining adequate seizure duration differed depending on the subject group. Whenever the EEG seizure duration shortened to between 20 and 30 seconds, one of the following changes was made at the next ECT treatment to lengthen the seizure: a) for the caffeine group, the dose of caffeine was increased by 242 mg (one 2-cc vial) or 2) for the group given stimulus intensity dosing, the standard clinical approach of increasing stimulus intensity by approximately 30% was used. Whenever a subject in either group experienced an EEG seizure of less than 20 seconds, stimulus charge was immediately increased by approximately 30% and the patient restimulated within 30–45 seconds. For both the caffeine group and the group given stimulus intensity dosing, whenever an EEG seizure greater than 100 seconds occurred, stimulus charge was reduced by approximately 30% at the next ECT treatment session.

### *Clinical Ratings*

Subjects were defined as ECT responders if they achieved a score of 3 (mildly ill) or less on a 7-point Clinical Global Impression (CGI) severity scale (14) completed 2–3 days after the last ECT treatment by a research psychiatrist (G.S.F.) blind to drug status (placebo versus caffeine). This CGI determination was supplemented by both observer-rated (Montgomery-Asberg Depression Rating Scale) (15) and self-rated (Carroll Self-Rating Depression Scale) (16) assessments of symptom severity in order to provide measures of concurrent validity.

All subjects were monitored during ECT for signs and symptoms of anxiety occurring from the time of the caffeine or placebo infusion until induction of anesthesia (about 3 minutes) by raters blind to drug status. The caffeine group and the group given stimulus intensity dosing were also compared on observer-rated (Covi Anxiety Scale) (17) and self-rated (Spielberger State Anxiety Scale) (18) anxiety scales before and 2–3 days after completion of the ECT course.

### *Adverse Effects*

Vital signs were obtained at 30, 60, 180, and 300 seconds after the ECT stimulus. For each interval, the rate-pressure product (the product of pulse times systolic blood pressure) was calculated to provide an index of myocardial oxygen consumption (workload) (19). The largest rate-pressure product during the 5-minute post-stimulus interval was taken as the maximal rate-pressure product. All subjects were also monitored with ECG.

Recovery of pre-ECT orientation was determined after each ECT treatment by trained nursing personnel using a standardized rating battery (20). Orientation was assessed at 30-minute intervals after the ECT stimulus for up to 2 hours until the patient had returned to pretreatment orientation status.

Memory impairment following the course of ECT was assessed by using the Russell revision (21) of the Wechsler Memory Scale. The memory scales were administered before beginning ECT and then repeated (using different versions of the same scales) 2–3 days after the last ECT treatment, before beginning continuation therapy. The difference (pre-ECT minus post-ECT) score was taken as the measure of interest.

After each ECT treatment, subjects were assessed for the occurrence of systemic side effects (headache, nausea, vomiting, muscle soreness, and psychomotor agitation) by nursing personnel using a standardized rating form.

### *Statistical Analyses*

Differences between continuous variables were evaluated with two-tailed *t* tests. Correlations were assessed with the Pearson product-moment correlation coefficient. Proportions for categorical variables were compared by using a Pearson chi-square test. In cases where the chi-square test was inappropriate due to insufficient cell size, Fisher's exact test was used. The nonparametric Wilcoxon two-sample test was used to compare the charge values for the caffeine group and the group given stimulus intensity dosing because this measure was not normally distributed.

## RESULTS

### *Effects of Caffeine Versus Stimulus Intensity Dosing on ECT Seizure Duration*

There were no significant differences between the caffeine group and the group given stimulus intensity dosing with respect to 1) mean seizure duration per ECT treatment ( $t=1.85$ ,  $df=38$ ,  $p=0.08$ ) or 2) mean cumulative seizure duration for the course of ECT treatments ( $t=0.34$ ,  $df=38$ ,  $p=0.74$ ) (see table 2). Over the treatment course, the group given stimulus intensity dosing required an average increase of 49%

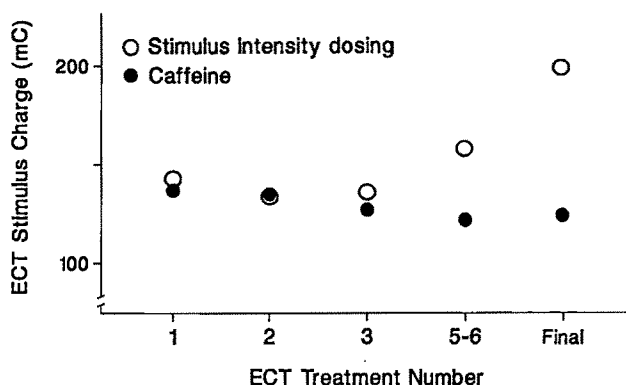
**TABLE 2. Clinical Effects of Caffeine-Modified ECT Versus Stimulus Intensity Dosing in 40 Depressed Inpatients**

Item	Caffeine Group (N=20)	Stimulus Intensity Dosing Group (N=20) <sup>a</sup>
Seizure duration per ECT treatment (sec)		
Mean	79.9	64.5
SD	31.0	20.0
Cumulative seizure duration (sec)		
Mean	619.90	595.35
SD	207.11	251.76
Number of ECT treatments		
Mean	8.2	9.4
SD	2.18	2.72
Range	5-14	5-18
Montgomery-Asberg Depression Rating Scale score		
Before ECT		
Mean	36.5	39.4
SD	7.10	8.15
After ECT		
Mean	12.3	13.4
SD	7.72	11.78
Carroll Self-Rating Depression Scale score		
Before ECT		
Mean	29.3	28.8
SD	7.63	9.75
After ECT		
Mean	9.3	7.4
SD	9.17	7.45
Covi Anxiety Scale score		
Before ECT		
Mean	9.5	9.0
SD	2.7	3.2
After ECT		
Mean	4.1	4.5
SD	2.2	2.2
Spielberger State Anxiety Scale score		
Before ECT		
Mean	63.1	60.4
SD	9.0	12.4
After ECT		
Mean	38.6	39.5
SD	11.6	12.9

<sup>a</sup>Three of these patients required caffeine pretreatment during their courses of ECT to maintain seizures of adequate duration.

in stimulus charge in order to maintain appropriate seizure duration (from 133.8 millicoulombs at the second ECT to 199.4 millicoulombs at the final ECT treatment) (see figure 1). These findings are consistent with previous data indicating that the seizure threshold increases during a course of ECT (1, 2, 5). In contrast, the mean stimulus charge for the caffeine group decreased by 7.9% (from 134.5 millicoulombs at the second ECT to 123.9 millicoulombs at the final ECT treatment) (see figure 1). Indeed, caffeine pretreatment allowed a reduction in stimulus charge in nine (45%) of the 20 subjects who received the medication. These data indicate that caffeine pretreatment can maintain seizure duration during a course of ECT even in the absence of increases in stimulus intensity.

For nine of the subjects who received caffeine pre-

**FIGURE 1. Mean ECT Stimulus Charges for Depressed Inpatients Given Stimulus Intensity Dosing (N=20) or Caffeine (N=20)<sup>a</sup>**

<sup>a</sup>The mean±SD stimulus charge was significantly greater for the group given stimulus intensity dosing than for the caffeine group at the fifth-sixth ECT treatment ( $157.3 \pm 80.8$  versus  $121.5 \pm 63.8$  millicoulombs, respectively;  $z = -2.04$ ,  $p < 0.04$ ) and at the final ECT treatment ( $199.4 \pm 130.9$  versus  $123.9 \pm 65.6$  millicoulombs, respectively;  $z = -2.15$ ,  $p < 0.03$ ).

treatment, brief seizures (20–30 seconds by EEG) occurred during the course of therapy despite the use of previously effective doses of caffeine. For these subjects an increase in the dose of caffeine at the next ECT treatment (N=10 of 143 ECT treatments) was effective at lengthening seizure duration and obviated the need for an increase in stimulus charge. The maximum amount of caffeine required at any ECT treatment was 726 mg (three 2-cc vials). In contrast, 11 of the patients in the group given stimulus intensity dosing required one or more (N=26 of 188 ECT treatments) increases in stimulus charge during the course of therapy to maintain adequate seizure length.

Among the 20 patients in the group given stimulus intensity dosing, nine (45%) required immediate re-stimulation at higher stimulus intensities because of missed or abortive seizures (19 seconds or less in duration by EEG criteria). For these patients, subsequent ECT treatments were administered at the higher stimulus intensities. In contrast, only four (20%) of the 20 patients in the caffeine group required immediate re-stimulation at higher stimulus intensities for short seizures. In each of these four patients, however, an increase in the dose of caffeine at the next ECT treatment lengthened the seizure duration appropriately, even though the stimulus intensity had been reduced to the initial dose used at the preceding treatment. As noted above, the maximum amount of caffeine required at any ECT treatment was 726 mg. Again, by increasing the dose of caffeine, the need for higher stimulus doses was obviated.

#### *Effects of Caffeine on Therapeutic Response to ECT*

Table 2 shows the effects of caffeine on therapeutic response to ECT. The criterion for response to ECT (CGI of mildly ill or less) was obtained in 19 (95%) of



the subjects in the caffeine group and 16 (80%) of the subjects in the group given stimulus intensity dosing. This high degree of therapeutic response was associated with parallel reductions in Montgomery-Asberg scale and Carroll scale scores in both groups. There were no differences between the caffeine group and the group given stimulus intensity dosing with respect to the rate of improvement on either of these depression rating scales. The mean $\pm$ SD number of ECT treatments was similar for the caffeine group and the stimulus intensity dosing group (see table 2).

During the course of ECT, three subjects in the group given stimulus intensity dosing experienced brief seizures despite maximal stimulus settings on the Mecta SR-1 device. At that time (mean of 8.3 ECT treatments), two of the three subjects satisfied our criteria for responder status. However, in each case the subject's clinical treatment team requested further ECT because a plateau in clinical improvement had not yet occurred. Therefore, all subsequent ECT treatments (mean of 2.3 per patient) were modified with caffeine pretreatment (242 mg), which resulted in seizures of adequate duration (mean duration for the first caffeine-modified ECT seizure was 48 seconds, versus 23 seconds for the previous ECT seizure not modified by caffeine). Each such subject showed further improvement in their depression rating scale scores. In addition, the subject who was previously a nonresponder eventually met responder criteria. Although the use of caffeine in the group given stimulus intensity dosing represented a deviation from the study protocol, data from these three subjects were included because the number of caffeine-modified treatments was modest and because the nature of the confounding effects would have tended to minimize (rather than exaggerate) intergroup differences in seizure duration and therapeutic response.

At the request of their clinical treatment team, seven subjects were switched during their course of treatment from right unilateral to bilateral ECT because of poor therapeutic response. Three subjects in the caffeine group were switched to bilateral ECT after a mean of 8.3 right unilateral ECT treatments (range=7–10) and received an average of 2.3 additional ECT treatments (range=1–4). All three patients eventually met criteria for responder status. Four subjects in the group given stimulus intensity dosing were switched to bilateral ECT after a mean of 7.25 ECT treatments (range=6–11) and received an average of five additional ECT treatments (range=2–7). Only two of these patients, however, eventually satisfied criteria for responder status.

### *Cognitive Side Effects of ECT*

In both the caffeine group and the group given stimulus intensity dosing, the majority of subjects recovered their pre-ECT orientation within 60 minutes after the second (83% and 77%, respectively), fifth–sixth (89% and 75%, respectively) and final (90% and

70%, respectively) ECT treatments. Follow-up memory testing was obtained 2–3 days after the last ECT treatment in 36 of the 40 subjects; the remaining four subjects (two in each group) either refused or were unable to complete the testing. There were no significant differences between the caffeine group and the group given stimulus intensity dosing with respect to mean $\pm$ SD items recalled on either the delayed verbal (2.22 $\pm$ 6.52 versus 3.50 $\pm$ 6.83, respectively) or delayed figural (1.67 $\pm$ 3.4 versus 1.44 $\pm$ 3.70, respectively) memory scales.

### *Other Potential Adverse Effects*

For both the caffeine group and the group given stimulus intensity dosing, the ECT treatments were associated with large increases in the rate-pressure product, although the percentage increase tended to diminish over the course of therapy. The mean $\pm$ SD increase in rate-pressure product was significantly greater in the caffeine group (140% $\pm$ 63%) than in the group given stimulus intensity dosing (82% $\pm$ 63%) for the second ECT treatment ( $t=2.92$ ,  $df=38$ ,  $p=0.006$ ) but not for the fifth–sixth treatments (110% $\pm$ 86% versus 83% $\pm$ 45%, respectively) or the final treatment (96% $\pm$ 76% versus 64% $\pm$ 53%, respectively). The difference in hemodynamic response at the second ECT treatment became nonsignificant, however, when subjects receiving antihypertensive medications (four in the caffeine group and seven in the group given stimulus intensity dosing) were deleted from the analysis. There were too few subjects in the caffeine group with hypertensive cardiovascular disease to determine its relationship to change in rate-pressure product during ECT.

For the caffeine group, there was a significant negative correlation ( $r=-0.46$ ,  $p=0.04$ ) between baseline caffeine intake and maximal rate-pressure product for the second ECT treatment but not for the fifth–sixth or the final treatment. Subjects with the lowest baseline caffeine intake tended to have the largest increases in rate-pressure product during the second ECT treatment. In contrast, there was no relationship between baseline caffeine intake and increase in rate-pressure product during any ECT treatment for subjects in the group given stimulus intensity dosing.

Seizures lasting longer than 200 seconds occurred during three (2%) of the 143 ECT treatments modified by caffeine and during two (1%) of the 188 ECT treatments in the group given stimulus intensity dosing. In two of the patients given caffeine, the seizures ended spontaneously (after 216 seconds and 233 seconds, respectively), and in the third the seizure was terminated at 236 seconds with intravenous methohexital. In the group given stimulus intensity dosing, both of the prolonged seizures (203 seconds and 212 seconds) ended spontaneously. The prolonged seizures were not associated with any adverse sequelae, including hypoxia, aspiration, or cardiovascular compromise. Prolonged

seizures at subsequent ECT treatments were avoided by a reduction in stimulus charge.

Acute infusion-related anxiety was observed in four subjects in the caffeine group and in none of those in the group given stimulus intensity dosing. In general, the symptoms were mild and never severe enough to necessitate dropping the patient from the protocol. There was no apparent relationship between the occurrence of infusion-related anxiety and the anxiety scale ratings before beginning ECT. On completion of the ECT course, both the caffeine group and the group given stimulus intensity dosing showed reductions in anxiety ratings that paralleled their overall clinical improvement (see table 2).

There were no apparent differences between the caffeine group and the group given stimulus intensity dosing with respect to the occurrence of systemic side effects, including headache, nausea, vomiting, muscle soreness, and agitation.

## DISCUSSION

Our results demonstrate that caffeine pretreatment is an effective alternative to stimulus intensity dosing for the maintenance of seizure duration during pulse unilateral nondominant ECT. Of interest, the use of lower stimulus doses with caffeine-modified ECT did not appear to limit the clinical efficacy of the therapy. Indeed, there was a trend toward a higher response rate for the caffeine group (95% versus 80%), even though that group received an average of 1.2 fewer ECT treatments. In addition, three patients in the group given stimulus intensity dosing eventually required caffeine pretreatment because of brief seizures at maximal stimulus settings; in each case the caffeine-modified ECT was associated with further clinical improvement.

The therapeutic efficacy of caffeine-modified ECT may have important implications for a mechanism of action of ECT. As noted above, several lines of evidence suggest that low-intensity ECT stimuli may be less efficacious than higher stimulus doses, even if seizures of "adequate duration" have been elicited (6–8, 22–24). This apparent therapeutic advantage for high-energy ECT stimuli has been attributed to greater seizure generalization with more intense stimulation of relevant brain regions (e.g., the diencephalon) (9) and/or systems (e.g., endogenous inhibitory mechanisms) (24). It is possible that the intensity and/or extent of generalization of ECT seizures may be enhanced pharmacologically by pretreatment with caffeine, thereby allowing for relatively lower stimulus doses without loss of clinical efficacy. We hope to test this hypothesis with an examination of the effects of caffeine on the neuroendocrine (e.g., prolactin), electroencephalographic, and cerebral blood flow correlates of ECT seizures. Whether these potential effects are mediated by the direct cerebral stimulant action of caffeine (25), through effects on adenosine (25) or benzodiazepine

(26) receptors, or through still other mechanisms will also need to be determined.

The use of caffeine during ECT was not complicated by any clinically significant adverse effects. Although in some subjects caffeine pretreatment was associated with a greater hemodynamic response following the induced seizure, in no case were the changes associated with any clinically significant sequelae (e.g., ECG changes, cardiac arrhythmia, or complaints of chest pain after ECT). Cardiovascular tolerance to caffeine is known to develop rapidly (27), and, consistent with this finding, we observed that the hemodynamic response to caffeine lessened over the course of ECT treatments. In addition, patients with relatively lower baseline caffeine intake tended to exhibit the greatest hemodynamic response to their first caffeine-modified ECT, again suggesting that drug tolerance may play a role in the hemodynamic response to caffeine-modified ECT.

There were no major differences between the caffeine group and the group given stimulus intensity dosing with respect to cognitive side effects from the ECT. In contrast, Shapira et al. (3) reported a nonsignificant trend for longer reorientation times after caffeine-modified than after non-caffeine-modified ECT treatments in eight patients who served as their own controls. The caffeine treatments were also associated with poorer performance on two measures of "design recognition." These data are not directly comparable to our own findings, however, because 1) stimulus charge was invariant for the caffeine-modified and the non-caffeine treatments, and, as a result, 2) seizure duration was significantly longer for the former. Since seizure duration may be correlated with amnesic side effects after unilateral nondominant ECT (28), it appears possible that the longer seizures observed with the caffeine treatments may have accounted for the observed cognitive changes. These findings and our own observations suggest that any beneficial effects of caffeine on cognitive side effects from ECT may be diminished if seizure duration is excessive (3). Future studies of caffeine pretreatment versus stimulus intensity dosing should incorporate more sensitive measures of memory functioning in order to help resolve this issue.

In summary, caffeine pretreatment permitted the continued use of comparatively low stimulus intensities over a course of ECT, without loss of clinical efficacy. These results may have important implications for understanding the mechanism of action of ECT, and they suggest the need for further studies of the impact of caffeine pretreatment on cognitive side effects that may be associated with high-intensity ECT stimuli.

## REFERENCES

1. Coffey CE, Weiner RD, Hinkle PE, et al: Augmentation of ECT seizures with caffeine. *Biol Psychiatry* 1987; 22:637–649
2. Hinkle PE, Coffey CE, Weiner RD, et al: Use of caffeine to

- lengthen seizures in ECT. *Am J Psychiatry* 1987; 144:1143–1148
3. Shapira B, Lerer B, Gilboa D, et al: Facilitation of ECT by caffeine pretreatment. *Am J Psychiatry* 1987; 144:1199–1202
  4. Lerer B, Shapira B, Kindler S, et al: Pharmacological manipulation of seizure duration: a new direction in ECT technology, in *New Directions in Affective Disorders*. Edited by Lerer B, Gershon S. New York, Springer-Verlag (in press)
  5. Sackeim HA, Decina P, Prohovnik I, et al: Seizure threshold in electroconvulsive therapy. *Arch Gen Psychiatry* 1987; 44:355–360
  6. Ottosson JO: Experimental studies on the mode of action of electroconvulsive therapy. *Acta Psychiatr Neurol Scand Suppl* 1960; 145:1–141
  7. Sackeim HA, Decina P, Kanzler M, et al: Effects of electrode placement on the efficacy of titrated, low-dose ECT. *Am J Psychiatry* 1987; 144:1449–1455
  8. Robin A, De Tissera S: A double-blind controlled comparison of the therapeutic effects of low and high energy electroconvulsive therapies. *Br J Psychiatry* 1982; 141:357–366
  9. Abrams R: A hypothesis to explain divergent findings among studies comparing the efficacy of unilateral and bilateral ECT in depression. *Convulsive Therapy* 1986; 2:253–257
  10. Weiner RD, Coffey CE: Minimizing therapeutic differences between bilateral and unilateral nondominant ECT. *Convulsive Therapy* 1986; 2:261–265
  11. Lane JD: Caffeine abuse and caffeine reduction, in *Applications in Behavioral Medicine and Health Psychology: A Clinician's Source Book*. Edited by Blumenthal JA, McKee DC. Sarasota, Fla, Professional Resource Exchange, 1987
  12. d'Elia G: Unilateral ECT. *Acta Psychiatr Scand Suppl* 1970; 215:5–98
  13. Sackeim HA, Decina P, Portnoy S, et al: Studies of dosage, seizure threshold, and seizure duration in ECT. *Biol Psychiatry* 1987; 22:249–268
  14. Guy W (ed): *ECDEU Assessment Manual for Psychopharmacology*: Publication ADM 76-338. Rockville, Md, US Department of Health, Education and Welfare, 1976
  15. Montgomery SA, Asberg M: A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979; 134:382–389
  16. Carroll BJ, Feinberg M, Smouse PE, et al: The Carroll Rating Scale for Depression, I: development, reliability and validation. *Br J Psychiatry* 1981; 138:194–200
  17. Covi L, Lipman RS, McNair D, et al: Symptomatic volunteers in multicenter drug trials. *Progress in Neuropsychopharmacology* 1979; 3:521–533
  18. Spielberger CD: *The State-Trait Anxiety Scale*. Palo Alto, Calif, Consulting Psychologists Press, 1977
  19. Jones RM, Knight PR, Hill AB: Rate pressure product (letter). *Anesthesia* 1980; 35:1010–1011
  20. Daniel WF, Crovitz HF: Disorientation during electroconvulsive therapy, in *Electroconvulsive Therapy: Clinical and Basic Research Issues*. Edited by Malitz S, Sackeim HA. New York, Annals of the New York Academy of Science, 1986
  21. Russell EW: A multiple scoring method for the assessment of complex memory functions. *J Consult Clin Psychol* 1975; 43: 800–809
  22. Cronholm B, Ottosson JO: Ultrabrief stimulus technique in electroconvulsive therapy. *J Nerv Ment Dis* 1963; 137:117–123
  23. Price TRP, McAllister TW: Response of depressed patients to sequential unilateral nondominant brief pulse and bilateral sinusoidal ECT. *J Clin Psychiatry* 1986; 47:182–186
  24. Sackeim HA: Mechanism of action of electroconvulsive therapy, in *American Psychiatric Press Review of Psychiatry*, vol 7. Edited by Francis AJ, Hales RE. Washington, DC, American Psychiatric Press, 1988
  25. Snyder SH, Sklar P: Behavioral and molecular actions of caffeine: focus on adenosine. *J Psychiatr Res* 1984; 18:91–106
  26. Marangos PJ, Martino AM, Paul SM, et al: The benzodiazepines and inosine antagonize caffeine-induced seizures. *Psychopharmacology* 1981; 72:269–273
  27. Myers MG: Effects of caffeine on blood pressure. *Arch Intern Med* 1988; 148:1189–1193
  28. Miller AL, Faber RA, Hatch JP, et al: Factors affecting amnesia, seizure duration, and efficacy in ECT. *Am J Psychiatry* 1985; 142:692–696



# Gender Weighting of *DSM-III-R* Personality Disorder Criteria

June Sprock, Ph.D., Roger K. Blashfield, Ph.D., and Brenda Smith, B.A.

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*This study explored the gender weighting of the diagnostic criteria for personality disorders. Gender weighting was defined in terms of how 33 female and 17 male nonclinicians ranked the diagnostic criteria along a male-female dimension. Although the a priori expectation was that antisocial would be the prototypically masculine personality disorder and histrionic the feminine, the subjects ranked criteria from the sadistic category as the most masculine and those from the dependent category as the most feminine. These results and the subjects' gender weighting of criteria for borderline, obsessive-compulsive, and self-defeating personality disorders are analyzed in detail.*

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Classification of the personality disorders has been controversial, and the *DSM-III* and *DSM-III-R* criteria are no exceptions. Criticisms concerning the poor reliability of the *DSM-III* personality disorder criteria resulted in an attempt to provide more behaviorally specific definitions in *DSM-III-R*. However, critics continue to point out the overlapping criteria for disorders, to note the difficulty in distinguishing between personality traits and disorders, and to advocate alternative models such as dimensional systems (1).

Another major area of controversy has been the possibility of sex bias in the symptoms that constitute each category. Clinicians more frequently give women diagnoses of histrionic, dependent, and borderline personality disorders and give men diagnoses of paranoid, antisocial, and compulsive personality disorders (2). According to Kaplan (2), the *DSM-III* diagnostic criteria contain male biases about which behaviors are pathological and which are healthy. As a result, the behavior of healthy women may be labeled as "sick."

In a rebuttal to the Kaplan article, Kass et al. (3) presented data from two samples showing that women do have a higher incidence of histrionic and dependent personality disorders and that men have a higher rate of antisocial personality disorder. In one sample, men

also had a higher frequency of schizoid and passive-aggressive personality disorders, while in the other sample, men had a higher rate of paranoid personality disorder. Kass et al. claimed that the finding of higher rates of these disorders in men argued against a bias against women in the *DSM-III* criteria. On the other hand, Reich (4) found a greater incidence of histrionic personality disorder in women and of paranoid, obsessive-compulsive, and antisocial personality disorders in men but failed to find higher rates of dependent or borderline disorder in women.

A study conducted by Warner (5) suggested that clinicians demonstrate a gender bias in assigning personality diagnoses; that is, they will assign different diagnoses on the basis of the gender of the patients even though the symptoms are identical. In this study, he presented a case that included a variety of signs and symptoms of psychopathology. Two versions of the case were constructed that differed only in using masculine pronouns (e.g., "he," "his") or feminine pronouns (e.g., "she," "her") to describe the patient. When the case was presented as that of a woman, the most frequent diagnosis was hysterical personality disorder, whereas diagnoses were equally divided between antisocial and hysterical personality disorders when the same case was presented as that of a man.

Recently, Ford and Widiger (6) examined the role of gender bias and actual differences in base rates of antisocial and histrionic personality disorders in men and women. They used nine cases in which the patients, who had varying numbers of symptoms from the histrionic and antisocial categories, were presented as male or female. Over 300 psychologists were asked either to assign diagnoses or to rate the degree to which the patients met each of the criteria for antisocial or histrionic personality disorder. Ford and Widiger found gender bias in the assignment of diagnoses but not in the symptom ratings, suggesting that the bias may be associated with the diagnostic labels themselves, not the criteria.

Henry and Cohen (7) conducted two studies to examine the role of labeling processes in the overrepresentation of the diagnosis of borderline personality disorder among women. In the first study, they used Warner's method (5) for a case of borderline personality disorder taken from the *DSM-III Casebook* (8); they failed to find a significant difference in the diagnosis of borderline personality disorder between the two versions of the case. However, they hypothesized that labeling processes may play more of a role in a

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Received Sept. 28, 1988; revision received Oct. 17, 1989; accepted Nov. 8, 1989. From the Psychology Department, Indiana State University, Terre Haute. Address reprint requests to Dr. Blashfield, Box J-256, JHMHC, University of Florida, Gainesville, FL 32610-0256.

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natural setting (i.e., with a real patient rather than a brief case vignette) and in cases in which there is less severe (i.e., less obvious) pathology. In the second study, a large group of undergraduate students was asked to rate the presence of 24 symptoms of borderline personality disorder in normal men and women. Contrary to expectation, the mean ratings, which reflected both frequency and severity, were significantly higher for men than for women on 22 of the 24 items. The authors hypothesized that the symptoms of borderline personality disorder may be seen as more congruent with the male sex role and as less tolerable (i.e., more pathological) in women. They concluded that labeling processes with respect to gender roles did contribute to the assignment of the diagnosis of borderline personality disorder.

Concerns regarding sex bias are also evident in the placement of self-defeating and sadistic personality disorders in an appendix, "Proposed Diagnostic Categories Needing Further Study," in *DSM-III-R*. The controversy first arose when the masochistic personality disorder category was proposed. Women's rights advocates felt that the category was biased against women because it would primarily be used as a diagnosis for women and could be used to classify victims of assault and abuse as mentally ill. Complaints came from the women's committees of both the American Psychological Association and the American Psychiatric Association. In addition, the National Coalition Against Domestic Violence reportedly considered a lawsuit (9). Attempts were made to address these concerns by changing the name from masochistic to self-defeating personality disorder and changing the focus of the symptoms to negative consequences brought on by the individual's own behavior rather than perpetrated by others. Sadistic personality disorder was added because it was argued that individuals who inflict harm on others also have a personality disorder. Nevertheless, self-defeating personality disorder has remained a controversial category. Critics have argued that neither category is supported by empirical evidence and that the sadistic category was simply added to counterbalance masochistic personality disorder (9).

A study by Fuller and Blashfield (10) attempted to examine the role of gender bias when clinicians assign the diagnosis of masochistic personality disorder. Using a method similar to Warner's (5), they investigated whether gender plays a role when this diagnosis is assigned. Five cases representing masochistic personality disorder were constructed from the literature and the criteria in the second draft of *DSM-III-R*. As in the Warner study, half of the clinicians received a version of the cases presented as if the patients were male, and the other half received identical cases except that the patients were portrayed as female. This study found no significant differences in the diagnoses for any of the cases on the basis of the sex of the patients.

While there appears to be a gender difference in the diagnosis of personality disorders, the reason for this difference is not clear. Is it because of gender weighting

of the diagnostic criteria, a difference in the prevalence of some disorders, the presence of gender-related stereotypes associated with the different disorders, or a combination of these and other unknown causes? In this research study, differences in gender weighting for the diagnostic criteria for personality disorders were examined. Gender weighting was defined in terms of the degree to which nonclinicians saw the behaviors described in the criteria as varying along a male-female dimension. Differences in gender weighting may reflect the sex role stereotyping that is common in society. Sex roles stipulate certain behaviors by men and other behaviors by women. If this sex role typing influences the diagnostic criteria for personality disorders, it should be evident among subjects who are unfamiliar with the personality disorders and the gender differences in the prevalences of these disorders. More specifically, in this study it was hypothesized that some *DSM-III-R* criteria for personality disorders would be seen as more feminine by nonclinicians, while other criteria would be viewed as more masculine. In particular, it was hypothesized that the diagnostic criteria for histrionic personality disorder would be rated as the most feminine and the criteria for antisocial personality disorder the most masculine.

## METHOD

Fifty undergraduate students (33 female, 17 male) enrolled in an introductory psychology course served as volunteer subjects for the study. For most of the participants (47 of 50), this was their first college psychology course. No subjects were familiar with *DSM-III-R* or the criteria for personality disorders. The participants' ages ranged from 18 to 25 years (mean age = 18.67). Thirty-seven were first-year college students, 10 were second-year, two were third-year, and one was a fourth-year student. All of the subjects received extra credit in their psychology course in return for their participation in the study.

The stimuli consisted of 142 3×5 index cards, each containing one of the *DSM-III-R* criteria for the 13 personality disorders (including self-defeating and sadistic). A criterion was operationally defined as any clause or phrase that was designated by a number or letter in *DSM-III-R*. Exclusionary criteria were not presented.

The subjects were presented the 142 index cards in random order and were asked to sort the cards along a dimension of gender from features most characteristic of men to those most typical of women. They were free to sort the criteria into as many categories as they felt were appropriate. After being seated at tables in small groups and signing the consent forms, the participants were read the instructions. The procedure was untimed and lasted approximately 45 minutes to 1 hour. Afterward, the purpose and procedures involved were explained, and questions were answered. The order and grouping of the cards were recorded immediately.

The symptoms were assigned a value from 0 (most

**TABLE 1.** Rank Ordering of *DSM-III-R* Personality Disorders by 33 Female and 17 Male Nonclinician Raters According to Their Association of Gender With the Criteria

Personality Disorder	Rank Order <sup>a</sup>					
	Overall		Male Raters		Female Raters	
	Mean	SD	Mean	SD	Mean	SD
Sadistic	0.202	0.090	0.208	0.102	0.200	0.093
Antisocial	0.314	0.136	0.348	0.144	0.296	0.137
Schizoid	0.386	0.111	0.399	0.125	0.379	0.111
Passive-aggressive	0.418	0.059	0.381	0.072	0.437	0.073
Obsessive-compulsive	0.481	0.150	0.456	0.155	0.493	0.157
Paranoid	0.482	0.117	0.476	0.133	0.486	0.112
Narcissistic	0.483	0.132	0.478	0.099	0.485	0.154
Self-defeating	0.503	0.080	0.515	0.079	0.498	0.088
Schizotypal	0.509	0.095	0.503	0.076	0.512	0.108
Borderline	0.547	0.153	0.555	0.162	0.543	0.154
Avoidant	0.587	0.119	0.599	0.112	0.580	0.130
Histrionic	0.611	0.149	0.621	0.100	0.606	0.180
Dependent	0.696	0.104	0.669	0.116	0.710	0.106

<sup>a</sup>0.000=most strongly associated with masculine behavior; 1.000=most strongly associated with feminine behavior.

characteristic of men) to 1 (most characteristic of women) for each subject according to their placement along the continuum. On the basis of the sortings across subjects, means were calculated for each of the 142 symptoms and for each diagnosis. Separate means were also calculated according to the sex of the subject in order to examine sex differences between the male and female subjects.

## RESULTS

The mean symptom rankings for each disorder showed that dependent personality disorder was seen as the most characteristically feminine, followed by histrionic and avoidant personality disorders. Sadistic personality disorder was seen as the most typical of men, followed by antisocial and schizoid personality disorders. Disorders that fell near the middle (i.e., were not seen as particularly masculine or feminine) were obsessive-compulsive, paranoid, self-defeating, and schizotypal (see table 1).

Examination of the rank order means for individual criteria within disorders revealed several interesting findings. Several diagnostic criteria for "feminine" disorders had been sorted as more characteristic of men. In particular, two histrionic features ("is self-centered, actions being directed toward obtaining immediate satisfaction; has no tolerance for the frustration of delayed gratification" and "has a style of speech that is excessively impressionistic and lacking in detail") and two avoidant symptoms ("has no close friends or confidants [or only one] other than first-degree relatives" and "fears being embarrassed by blushing, crying, or showing signs of anxiety in front of other people") had mean ratings of less than 0.500. Examination of the disorders seen as the most masculine revealed that one schizoid criterion ("indicates little if any desire to have sexual experiences with another person") was seen as a feminine trait. It is interesting that the cluster of

antisocial items relating to inadequate parenting skills was rated as the most feminine of the antisocial criteria, although it was still on the male side of the continuum. All criteria associated with dependent and sadistic personality disorders—the two disorders most strongly associated with gender roles—were rated in the direction consistent with their overall mean.

Mean rankings of the diagnoses were not significantly different for the male and female participants ( $t=1.27$ ,  $df=12$ , *n.s.*), and there was only minimal variability in their rankings of individual symptoms (see table 1).

Symptoms seen as most strongly associated with male or female gender stereotypes were examined. Diagnostic criteria with a rank order mean less than 0.200 were used to construct the male stereotype, and criteria with a mean greater than 0.800 were selected for the female stereotype. The resulting stereotypic woman with a personality disorder was someone who is uncomfortable and helpless when alone and is easily hurt by criticism; the stereotypic man was cruel, angry, and aggressive (see table 2). All of the symptoms from the male stereotype came from sadistic personality disorder, except for one that came from the borderline category. The four criteria that constituted the female stereotype came from three different disorders.

We attempted to look at the consistency with which the subjects assigned ratings. Several symptoms are sufficiently similar to allow an examination of consistency. Symptoms suggestive of restricted affect (criterion 7 for obsessive-compulsive, criteria 3 and 7 for schizoid) were ranked similarly (0.236, 0.242, and 0.281, respectively), as were symptoms revolving around fear of abandonment (criterion 8 for borderline, criterion 8 for dependent) (0.715 and 0.753, respectively). Similar rankings were also given to symptoms related to the need for attention (0.560 for criterion 5 for histrionic and 0.666 for criterion 7 for narcissistic). Overall, subjects appeared to be quite consistent in judging the gender association of symptoms.

TABLE 2. Criteria for *DSM-III-R* Personality Disorders Ranked as the Most Masculine and the Most Feminine by 50 Nonclinicians

Symptom	Rating <sup>a</sup>		DSM-III-R Disorder for Which Symptom Is a Criterion
	Mean	SD	
Most masculine			
Is fascinated by violence, weapons, martial arts, injury, or torture	0.077	0.147	Sadistic
Has used physical cruelty or violence for the purpose of establishing dominance in a relationship	0.104	0.161	Sadistic
Gets other people to do what he or she wants by frightening them (through intimidation or even terror)	0.130	0.160	Sadistic
Cruel, demeaning, and aggressive behavior	0.133	0.187	Sadistic
Inappropriate, intense anger or lack of control of anger, e.g., frequent displays of temper, constant anger, recurrent physical fights	0.150	0.193	Borderline
Is amused by, or takes pleasure in, the psychological or physical suffering of others (including animals)	0.191	0.239	Sadistic
Most feminine			
Feels devastated or helpless when close relationships end	0.845	0.199	Dependent
Is overly concerned with physical attractiveness	0.819	0.279	Histrionic
Feels uncomfortable or helpless when alone, or goes to great lengths to avoid being alone	0.801	0.198	Dependent
Is easily hurt by criticism or disapproval	0.784	0.250	Dependent, avoidant

<sup>a</sup>0.000=most strongly associated with masculine behavior; 1.000=most strongly associated with feminine behavior.

## DISCUSSION

Naive participants demonstrated differences in the gender weighting that they associated with *DSM-III-R* criteria for the personality disorders. However, the male-female dimension for these differences was not what we had expected. In discussions of sex bias, the antisocial type is often seen as the prototypical masculine personality disorder, whereas the histrionic type is usually interpreted as the prototypical feminine personality disorder. Undergraduate subjects, however, did not see the gender weighting of personality disorder criteria as occurring along an antisocial-histrionic dimension but, instead, along a sadistic-dependent dimension.

These results are consistent with research on normal personality traits associated with men and with women. For example, when Rosenberg et al. (11) had college students sort 66 trait descriptors into masculine and feminine traits, women were seen as naive, submissive, and sentimental, and men were seen as dominant, critical, and unsocial. Ashmore's review of research on sex stereotypes and implicit personality theories (12) revealed that masculine and feminine personality traits could be represented according to two dimensions: a potency (controlling versus being controlled) and an evaluative (bad versus good) dimension. The female stereotype is "soft"—submissive and emotional—while the male stereotype is "hard"—dominant, aggressive, and unemotional. Given that personality disorders are sometimes viewed as extremes of normal personality traits, it is not surprising that the extreme of normal masculine aggressiveness and dominance is sadistic personality disorder, and the extreme of feminine passivity is dependent personality disorder.

One surprise, however, was the failure to find that the borderline personality disorder criteria were biased

toward giving that diagnosis to women. Prevalence data suggest that women are more likely to receive this diagnosis than men are (3, 13, 14). Examination of individual symptoms within the borderline personality disorder criteria reveals that one characteristic ("inappropriate, intense anger") was seen as strongly masculine, and all the others were generally seen as feminine, which pulled the overall mean for the category toward the middle of the continuum. When this "masculine" diagnostic criterion was dropped, the overall mean gender weighting for borderline personality disorder was 0.589. This one "masculine" symptom of borderline personality disorder was also part of the male personality disorder stereotype. One interesting speculation that can be drawn from this result is that men and women with borderline personality disorder present with different symptom patterns. The *DSM-III-R* polythetic criteria allow for heterogeneity in symptoms, so patients with the same diagnosis might present quite different symptom pictures. A woman with borderline personality disorder may be more likely to show dependency characteristics, whereas a man may appear as angry and aggressive.

Another diagnosis that was not seen as associated with gender was obsessive-compulsive personality disorder. We expected that the symptoms used to define this disorder would be seen as male sex role behaviors. While the overall mean rating fell near the middle of the continuum, ratings of individual criteria were quite variable. Three criteria (inability to discard worn-out objects, preoccupation with details and rules, inflexibility in matters of morality) were seen as feminine traits, two (restricted expression of emotion, lack of generosity in giving) were seen as masculine, and the remaining four symptoms were not seen as gender related. The view that the obsessive-compulsive person-



ality is biased toward masculine behaviors was not shown in this study.

Another interesting (albeit ironic) result concerned the two controversial diagnostic categories, sadistic and self-defeating personality disorders. When it was proposed as a category in the first version of *DSM-III-R*, masochistic personality disorder was criticized as having a potential female sex bias. As a result, the diagnostic category was revised and the disorder was renamed self-defeating; however, the category has continued to be criticized for gender bias. Our results showed that the diagnostic criteria for the self-defeating category had a neutral gender weighting, while sadistic personality disorder had the most extreme gender weighting.

Overall, the results of this study suggest gender weighting in the *DSM-III-R* diagnostic criteria for personality disorders. Whether this weighting is inappropriate and reflects gender bias is an issue that was not addressed in the study. Further research is needed to examine the influence of sex roles and gender bias on the diagnosis of personality disorders. In particular, we need to find innovative methodologies that can tease out the role of bias, gender weighting, and actual differences in the base rates of disorders in diagnostic labeling and in specific diagnostic criteria.

#### REFERENCES

1. Widiger TA, Frances A: The DSM-III personality disorders: perspectives from psychology. *Arch Gen Psychiatry* 1985; 42: 615-623
2. Kaplan M: A woman's view of DSM-III. *Am Psychol* 1983; 38:786-792
3. Kass F, Spitzer RL, Williams JBW: An empirical study of sex bias in the diagnostic criteria of DSM-III axis II personality disorders. *Am Psychol* 1983; 38:799-801
4. Reich J: Sex distribution of *DSM-III* personality disorders in psychiatric outpatients. *Am J Psychiatry* 1987; 144:485-488
5. Warner R: The diagnosis of antisocial and hysterical personality disorders: an example of sex bias. *J Nerv Ment Dis* 1978; 166: 839-845
6. Ford MR, Widiger TA: Sex bias in the diagnosis of histrionic and antisocial personality disorder. *J Consult Clin Psychol* 1989; 57:301-305
7. Henry KA, Cohen CI: The role of labeling processes in diagnosing borderline personality disorder. *Am J Psychiatry* 1983; 140:1527-1529
8. Spitzer RL, Skodol AE, Gibbon M, et al: *DSM-III Case Book*. Washington, DC, American Psychiatric Association, 1981
9. Holden C: Proposed new psychiatric diagnoses raise charges of gender bias. *Science* 1986; 231:327-328
10. Fuller AK, Blashfield RK: Masochistic personality disorder: a prototype analysis of diagnosis and sex bias. *J Nerv Ment Dis* 1989; 177:168-172
11. Rosenberg S, Nelson C, Vivekananthan PS: A multidimensional approach to the structure of personality impressions. *J Pers Soc Psychol* 1968; 9:283-294
12. Ashmore RD: Sex stereotypes and implicit personality theory, in *Cognitive Processes in Stereotyping and Intergroup Behavior*. Edited by Hamilton DL. Hillsdale, NJ, Lawrence Erlbaum Associates, 1981
13. Sheehy M, Goldsmith L, Charles E: A comparative study of borderline patients in a psychiatric outpatient clinic. *Am J Psychiatry* 1980; 137:1374-1379
14. Spitzer RL, Williams JBW: Borderline personality disorder: DSM-III approach, in *The Borderline Patient*. Edited by Friedel RA. New York, Biomedical Information Corp, 1981

# Oral S-Adenosylmethionine in Depression: A Randomized, Double-Blind, Placebo-Controlled Trial

Bruce L. Kagan, M.D., Ph.D., David L. Sultzer, M.D.,  
Nicholas Rosenlicht, M.D., and Robert H. Gerner, M.D.

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*Methylation has been implicated in the etiology of psychiatric illness. Parenteral S-adenosylmethionine, a methyl group donor, has been shown to be an effective antidepressant. The authors studied the antidepressant effect of oral S-adenosylmethionine in a randomized, double-blind, placebo-controlled trial for 15 inpatients with major depression. The results suggest that oral S-adenosylmethionine is a safe, effective antidepressant with few side effects and a rapid onset of action. S-Adenosylmethionine induced mania in a patient with no history of mania. S-Adenosylmethionine may be useful for patients who cannot tolerate tricyclic antidepressants. These findings support a role for methylation in the pathophysiology of depression.*

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Three lines of evidence implicate methylation in the etiology of psychiatric illness (see references 1 and 2 for reviews). First, administration of single large oral doses (10–20 g) of methionine, a precursor of S-adenosylmethionine (an important methyl group donor), causes acute psychosis in 40%–50% of patients diagnosed as “chronic schizophrenic” (3). These methionine studies were inspired by the observation that the chemical structures of various hallucinogens closely resembled those of methylated neurotransmitters and by the related hypothesis that schizophrenia might be due to an overactive methylation system (4). Second, low

blood levels of folate, a key intermediate in the methylation cycle, have been associated with several psychiatric illnesses, including depression, dementia, alcoholism, epilepsy, and organic psychosis (5, 6). Depression correlates most strongly with low folate levels. More severe affective illness and poorer treatment response are associated with low folate levels. Folate supplementation appears to speed and strengthen recovery from depression (7, 8). Third, S-adenosylmethionine, administered parenterally, has been demonstrated to be a safe and effective antidepressant with few side effects and a relatively rapid onset of action (9, 10; for review, see reference 11).

The many difficulties associated with parenteral administration have limited the clinical usefulness of S-adenosylmethionine and have also slowed research on this novel antidepressant. While S-adenosylmethionine is approved for clinical use in Italy, it has received little attention in this country. Recent trials in the United States have confirmed the effectiveness of parenteral S-adenosylmethionine (12–14), and preliminary studies have suggested that oral S-adenosylmethionine might be similarly effective (15, 16). We report here the results of a randomized, double-blind, placebo-controlled study of S-adenosylmethionine with depressed inpatients, which was designed to test whether oral S-adenosylmethionine could be a clinically useful antidepressant.

## METHOD

Informed consent was obtained from 18 patients between the ages of 18 and 65 years who met the *DSM-III* criteria for major depression, unipolar, without psychotic features and had scores on the Hamilton Rating Scale for Depression (21 items) (17) higher than 20. The trial was initially planned to include 30 patients, but we were forced to stop after 18 patients because approval of the 200-mg S-adenosylmethionine tablet was withdrawn by the U.S. Food and Drug Administration. This withdrawal was not related to the clinical performance of S-adenosylmethionine but to technical issues regarding data on the dissolution of the tablets.

All subjects were male inpatients consecutively ad-

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Received April 21, 1989; revisions received Aug. 9 and Sept. 28, 1989; accepted Oct. 31, 1989. From the Department of Psychiatry, West Los Angeles VA Medical Center; Department of Psychiatry, UCLA School of Medicine and UCLA Neuropsychiatric Institute; and UCLA Brain Research Institute. Address reprint requests to Dr. Kagan, Department of Physiology, UCLA School of Medicine, Center for the Health Sciences, 10833 Le Conte Ave., Los Angeles, CA 90024-1751.

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mitted to the clinical research center for affective disorders of the Brentwood Division of the West Los Angeles Veterans Administration Medical Center. Excluded from the study were actively suicidal, bipolar, and substance abuse patients, patients with significant medical problems, and patients who would suffer undue loss (e.g., financial) from participation in the trial. Physical examinations, routine laboratory studies (SMA-18, CBC, urinalysis, thyroid function tests), and ECGs were performed, and patients with major abnormalities were excluded. All patients underwent 7-day drug-free washouts on the ward and were rated again before entering the trial. Patients who no longer met the criteria for the study were excluded.

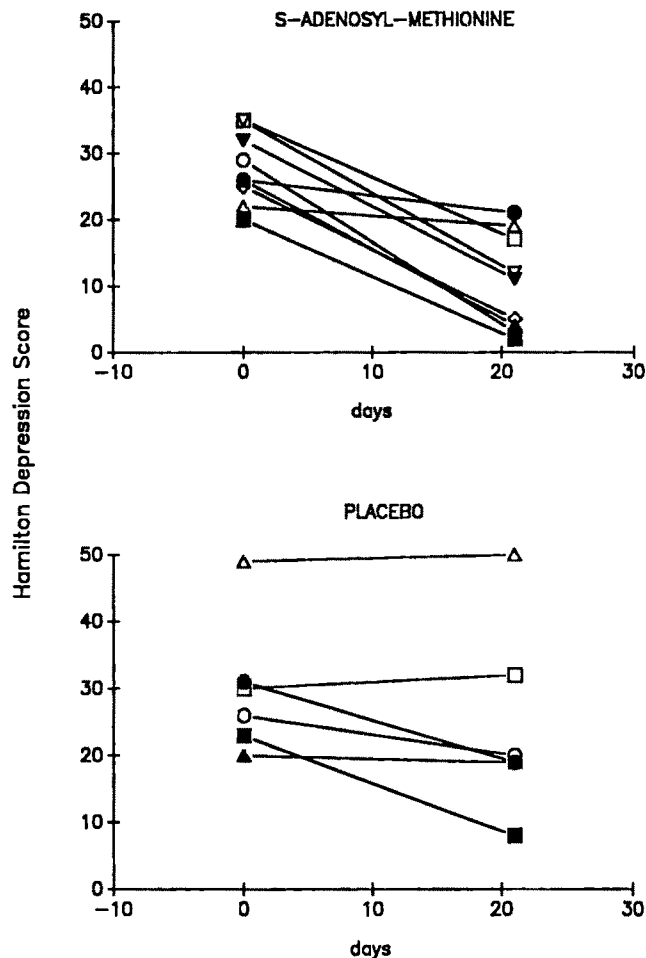
The patients were then randomly assigned (by means of a computer-generated random string of zeros and ones) to receive *S*-adenosylmethionine or placebo for 21 days. After the study, they spent 7 days without drugs in the hospital for observation and appropriate clinical intervention if needed. The laboratory tests and ECG were repeated at this time. A 21-day treatment period was chosen because most previous studies of *S*-adenosylmethionine have been limited to 21 days or less. Eighteen patients entered the trial, and 15 patients completed it. One patient (placebo) was withdrawn because of worsening depression and was treated with ECT. One patient (drug) was noncompliant and was dropped from the study. The other patient (placebo) was found to be hypothyroid and was dropped from the study and treated with thyroxine.

A double-blind design was employed; none of the investigators, ward staff, patients, or family members was aware of the code. The *S*-adenosylmethionine was in the form of 200-mg oral tablets, and the placebo tablets were identical in appearance. The first five patients received gradually increasing doses; placebo was given to two and *S*-adenosylmethionine to three, one of whom was later dropped because of noncompliance. Their doses increased from 200 mg/day to 800 mg b.i.d. (10:00 a.m. and 3:00 p.m.) by day 7. The dose remained 800 mg b.i.d. for days 8–21. Since the oral *S*-adenosylmethionine was extremely well tolerated by these first five patients, we decided to eliminate the graduated-dose phase of the study. Patients 6–18 were given 800 mg b.i.d. for the entire 21 days of the trial.

Hamilton depression ratings were done by the investigators at days 0, 3, 7, 14, and 21, and all of the subjects filled out the Carroll Rating Scale for Depression (18) at these times. Vital signs were recorded each day before the administration of the tablets. Mean Hamilton scores and mean Carroll scores for the two groups (drug and placebo) were analyzed according to a split-plot design and Tukey's test for multiple comparisons. Analysis of variance (ANOVA) was performed with a repeated measures design for drug versus placebo groups, change in scores over time, and Treatment by Time interaction.

The mean  $\pm$  SD age of the final 15 subjects was  $42.2 \pm 16.3$  years. Seven patients were black, seven pa-

FIGURE 1. Depressed Patients' Hamilton Depression Scores Before and After Treatment With Oral *S*-Adenosylmethionine or Placebo



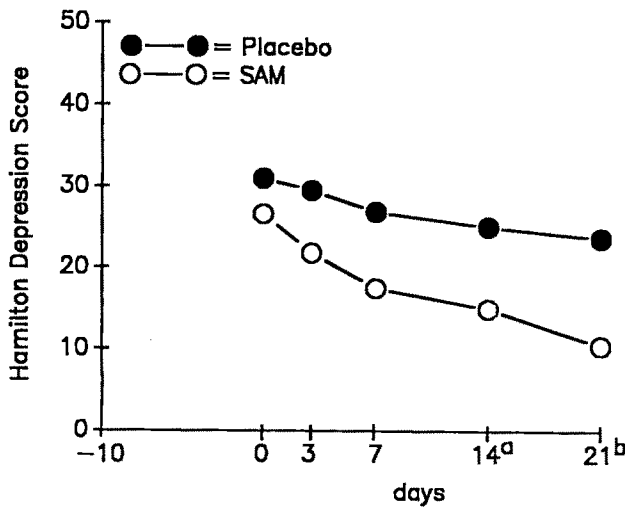
tients were white, and one patient was Hispanic. There were no significant differences between the *S*-adenosylmethionine and placebo groups in age or severity of illness (i.e., score on either the Hamilton or Carroll scale).

## RESULTS

The Hamilton scores for the 15 individual subjects before and after *S*-adenosylmethionine or placebo are shown in figure 1. Only one of the six placebo subjects experienced a reduction in Hamilton score of greater than 50% during the 21 days of the study. In the *S*-adenosylmethionine group, however, six of the nine patients had reductions of more than 50%.

The mean Hamilton scores for the two groups are shown in figure 2. The patients in the placebo group had an initial mean  $\pm$  SD score of  $31.0 \pm 8.5$ , which decreased to  $23.7 \pm 14.3$  over 21 days. Patients in the *S*-adenosylmethionine group had an initial mean score of  $26.6 \pm 5.5$  and a final score of  $10.4 \pm 6.9$ . The scores at day 0 for the two groups were not significantly dif-

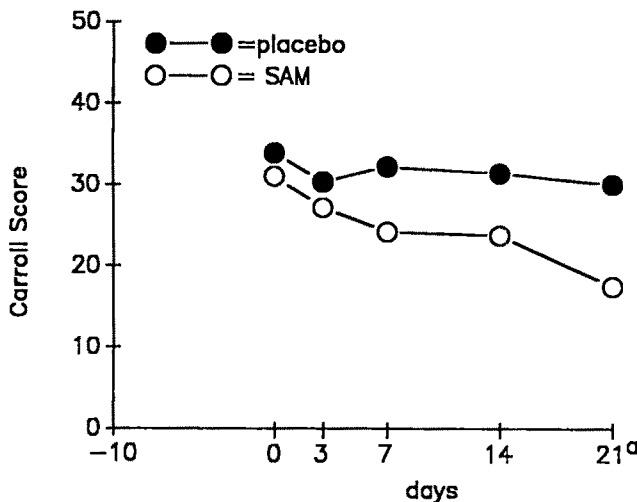
**FIGURE 2.** Depressed Patients' Mean Hamilton Depression Scores Over 21-Day Trial of Oral S-Adenosylmethionine (SAM) (N=9) and Placebo (N=6)



<sup>a</sup>Significant difference between groups ( $p < 0.05$ , Tukey's test).

<sup>b</sup>Significant difference between groups ( $p < 0.05$ , Tukey's test).

**FIGURE 3.** Depressed Patients' Mean Scores on Carroll Rating Scale for Depression Over 21-Day Trial of Oral S-Adenosylmethionine (SAM) (N=9) and Placebo (N=6)



<sup>a</sup>Significant difference between groups ( $p < 0.05$ , Tukey's test).

ferent. The mean Hamilton score for the S-adenosylmethionine group was significantly lower than that of the placebo group ( $p < 0.05$ , Tukey's test) at day 14 and day 21. While the score of the placebo group was not significantly different from baseline until day 14, the score of the S-adenosylmethionine group had significantly changed from baseline by day 7 ( $p < 0.01$ , Tukey's test).

Figure 3 shows the group mean scores for the Carroll depression self-rating scale. Initially, the drug and placebo group scores ( $31.0 \pm 4.5$  and  $33.8 \pm 5.5$ , respec-

tively) were not significantly different. The S-adenosylmethionine group score dropped more rapidly than that of the placebo group (to  $19.1 \pm 10.2$  and  $29.7 \pm 11.6$ ), and this difference became significant at day 21 ( $p < 0.05$ , Tukey's test). While the mean score of the placebo group never differed significantly from baseline, the score of the S-adenosylmethionine group had dropped significantly by day 7 ( $p < 0.05$ , Tukey's test).

The ANOVAs showed significant effects for drug versus placebo ( $F = 3.85$ ,  $df = 1, 13$ ,  $p = 0.07$ ) and change in scores over time ( $F = 21.9$ ,  $df = 4, 52$ ,  $p = 0.01$ ) and a significant Treatment by Time interaction ( $F = 2.36$ ,  $df = 4, 52$ ,  $p = 0.07$ ).

Oral S-adenosylmethionine was safe in our trial. No significant changes were noted in the posttrial results of the physical examination, routine laboratory studies, or ECG. Eleven side effects were reported during the trial, five by patients receiving S-adenosylmethionine and six by patients taking placebo. One patient receiving S-adenosylmethionine reported three of the five S-adenosylmethionine side effects: arm soreness; hot, itchy ear; and crawling sensation on the skin. Manic symptoms and headache were each experienced by one patient in the S-adenosylmethionine group. The symptoms reported by patients in the placebo group were flatulence ( $N = 2$ ), constipation ( $N = 2$ ), dry mouth ( $N = 1$ ), and light-headedness ( $N = 1$ ). All of the side effects were transient and mild with the exception of mania, which will be described. None of these minor side effects could be definitively attributed to S-adenosylmethionine, since they resolved spontaneously and did not require discontinuation of S-adenosylmethionine treatment.

We have no information about how the patients fared clinically after the trial. They were observed for side effects but were not rated after the trial. After the study the patients were treated with standard tricyclic antidepressants if treatment was clinically indicated.

On day 19 of treatment with S-adenosylmethionine, patient 2, a 65-year-old white man, was noted to be energetic, talkative, irritable, grandiose, and hyperkinetic. His clinical ratings had improved dramatically, but he was now noting the return of insomnia and decreased appetite. He left the ward against medical advice on day 21, completing the drug portion of the trial but refusing to stay for the 7-day observation period. He subsequently developed a manic episode characterized by pressured speech, flight of ideas, poor judgment, extensive travel, insomnia, decreased appetite, weight loss, and expenditure of large sums of money. He returned to the ward several weeks later and was successfully treated with lithium. However, he stopped taking his medication after discharge and had to be hospitalized 2 months later. Thus, even though S-adenosylmethionine treatment had been discontinued 3 months earlier, his manic episode persisted. Triggering by S-adenosylmethionine of a switch into mania has been reported previously (13, 19). Reinvestigation of the patient's history revealed only 1 prior depressive



episode (responsive to doxepin), no prior history of mania or hypomania, and a family history of depression but not mania.

## DISCUSSION

The results presented here strongly suggest that oral S-adenosylmethionine, like parenteral S-adenosylmethionine, is a safe, effective antidepressant with remarkably few side effects and a relatively rapid onset of action. Furthermore, our results are in accord with those of previous studies from Great Britain, Italy, and the United States. To our knowledge, this is the first demonstration of the effectiveness of oral S-adenosylmethionine in a double-blind, placebo-controlled trial.

Since previous studies (20, 21) have demonstrated that S-adenosylmethionine can be absorbed if administered orally, it is not unexpected that the oral form should be efficacious. If confirmed by other investigators, the finding that oral S-adenosylmethionine is an effective antidepressant could have significant clinical and research impact.

First, S-adenosylmethionine could prove to be a useful antidepressant for patients who cannot tolerate the side effects of standard tricyclic antidepressants. Candidates for such treatment are patients with cardiac arrhythmias, seizure disorders, narrow angle glaucoma, hypotension, constipation, and recent myocardial infarction, elderly patients, and patients who cannot be sedated. Furthermore, since S-adenosylmethionine may have a more rapid onset of action than standard tricyclics, it may be of use when a rapid recovery is essential, such as in the case of an acutely suicidal or catatonic patient. S-Adenosylmethionine may have potential in the treatment of other illnesses currently treated with tricyclic antidepressants, such as panic disorder, agoraphobia, bulimia, chronic pain syndromes, posttraumatic stress disorder, and attention deficit disorder. Trials involving patients with some of these illnesses are currently under way.

Since the chemical structure and biological activity of S-adenosylmethionine are unlike those of other antidepressants, it may be useful in the treatment of refractory depressions, either alone or in combination with a standard tricyclic agent or lithium.

Our results also confirm the experience of other investigators (19) that S-adenosylmethionine can induce mania and that the switch from depression to mania can be triggered in a patient with no previous history or family history of manic episodes.

While these prospects are exciting, it must be noted that our study has limitations. Our small patient sample restricts the certainty of our findings. Also, we studied a sample of unipolar depressed, male veteran inpatients. Whether the effects of S-adenosylmethionine are as great with women, nonveterans, or outpatients remains to be seen, although the results with parenteral administration are encouraging in this regard (10, 12–14). While our inpatient sample had a

partially controlled diet, we did not attempt to regulate the amounts of methionine or folate in the diet, and these nutrients may influence the efficacy of S-adenosylmethionine. The interaction of these two methyl group donors, S-adenosylmethionine and folate, has not yet been determined. Optimal dosage with oral S-adenosylmethionine also requires further study. While 1600 mg/day was well tolerated by all our patients, at least one (the oldest) was made manic by this dose. The three S-adenosylmethionine nonresponders (all younger than 50) may have needed higher doses to achieve therapeutic blood concentrations. We also know very little about the importance of dosage schedule or length of treatment. Our responders recovered quite rapidly, but many were still improving at the end of the 21-day trial. A longer trial might result in a higher percentage of recovered patients. Longer-term follow-up studies to assess relapse rate are also needed.

Perhaps the most exciting implications of the effectiveness of S-adenosylmethionine are those regarding the role of methylation in psychiatric illness. The original transmethylation hypothesis of schizophrenia postulated that schizophrenic patients have an overactive methylation system, which puts too many methyl groups on neurotransmitters during their metabolism, thus creating endogenous "psychotoxins" (4). While the search for these compounds was ultimately fruitless, this hypothesis inspired nearly a dozen studies of methionine loading, which all achieved the same finding: an oral challenge of 10 g of methionine (the immediate precursor of S-adenosylmethionine) causes 40%–50% of patients diagnosed as "chronic schizophrenic" to have acute, transient, reversible psychotic reactions without overt signs of organic delirium. This highly reproducible finding remains unexplained to this day. Our present results suggest an explanation. It seems possible that many of the patients then diagnosed as "chronic schizophrenic" might today be diagnosed as bipolar or schizoaffective. Thus, the 40%–50% psychosis rate found might represent a consistent rate of misdiagnosed bipolar and/or schizoaffective patients who experienced an acute manic psychosis in response to a challenge with methionine. It will be interesting to test this hypothesis with today's more stringent diagnostic criteria. A more modern version of the transmethylation hypothesis postulates an underactive methylation system in depression and an overactive system in mania (1). At least one study has found abnormalities in the activity of methionine adenosyltransferase (an enzyme involved in the synthesis of S-adenosylmethionine), which are consistent with this hypothesis (22).

The biological effects of S-adenosylmethionine are myriad, and it is difficult to determine which effects contribute to its therapeutic action. At least one report (23) has shown that S-adenosylmethionine influences monoamine metabolism, which could link its antidepressant effect to the monoamine theory of depression. However, its influence on phospholipid metabolism may be even more important in its antidepressant ef-

fect. S-Adenosylmethionine increases membrane fluidity, and this in turn can affect the functioning of receptors, ion channels, and second messenger systems (24). Indeed, S-adenosylmethionine has been shown to modulate the stimulation of phospholipid methylation by means of  $\beta$ -adrenergic agonists (25, 26), suggesting a possible common pathway where amines and S-adenosylmethionine might interact in depression.

We recommend that S-adenosylmethionine be given broader attention. Its potential utility in a wide variety of psychiatric disorders (e.g., alcoholism, dementia, epilepsy) (27) underlines the need for cautious, methodical research on this novel endogenous compound.

#### REFERENCES

1. Smythies JR: The transmethylation hypotheses of schizophrenia re-evaluated. *Trends in Neurosciences* 1984; 7:45-47
2. Reynolds EH, Stramentinoli G: Folic acid, S-adenosylmethionine and affective disorder. *Psychol Med* 1983; 13:705-710
3. Cohen SM, Nichols A, Wyatt R, et al: The administration of methionine to chronic schizophrenic patients: a review of ten studies. *Biol Psychiatry* 1974; 8:209-225
4. Osmond H, Smythies J: Schizophrenia: new approach. *J Ment Sci* 1952; 98:309-315
5. Reynolds EH, Preece JM, Bailey J, et al: A folate deficiency in depressive illness. *Br J Psychiatry* 1970; 117:287-292
6. Carney MWP: Serum folate values in 423 psychiatric patients. *Br Med J* 1967; 4:512-516
7. Coppen A, Abou-Saleh MT: Plasma folate and affective morbidity during long-term lithium therapy. *Br J Psychiatry* 1982; 141:87-89
8. Coppen AJ, Chandy S, Savade C: Folic acid enhances lithium prophylaxis. *J Affective Disord* 1986; 10:9-13
9. Fazio C, Andreoli V, Agnoli A, et al: Therapy of schizophrenia and depressive disorders with S-adenosyl-L-methionine. International Research Communication System (IRCS) Medical Science: Clinical Pharmacology and Therapeutics
10. Agnoli A, Andreoli V, Casacchia M, et al: Effect of s-adenosyl-l-methionine (SAMe) upon depressive symptoms. *J Psychiatr Res* 1976; 13:43-54
11. Baldessarini RJ: Neuropharmacology of S-adenosyl-L-methionine. *Am J Med* 1987; 83:95-103
12. Bell KM, Plon L, Bunney WE Jr, et al: S-Adenosylmethionine treatment of depression: a controlled clinical trial. *Am J Psychiatry* 1988; 145:1110-1114
13. Lipinski JF, Cohen BM, Frankenburg F, et al: Open trial of S-adenosylmethionine for treatment of depression. *Am J Psychiatry* 1984; 141:448-450
14. Janicak PG, Lipinski J, Davis JM, et al: S-Adenosylmethionine in depression: a literature review and preliminary report. *Ala J Med Sci* 1988; 25:306-313
15. Rosenbaum JF, Fava M, Falk WE, et al: Oral S-adenosylmethionine in major depression, in CME Syllabus and Scientific Proceedings in Summary Form, 141st Annual Meeting of the American Psychiatric Association. Washington, DC, APA, 1988
16. Kagan BL, Sultzer D, Rosenlicht N, et al: Oral S-adenosylmethionine versus placebo in depression. *Ibid*
17. Hamilton M: A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960; 23:56-62
18. Carroll BJ, Feinberg M, Smouse PE, et al: The Carroll Rating Scale for Depression, I: development, reliability and validation. *Br J Psychiatry* 1981; 138:194-200
19. Carney MWP, Martin R, Bottiglieri T, et al: The switch mechanisms in affective illness and SAM. *Lancet* 1983; 1:820-821
20. Stramentinoli G: S-Adenosyl-methionine as a drug, in *Biological Methylation and Drug Design*. Edited by Borchardt RT, Creveling CR, Veland PM. Clifton, NJ, Humana Press, 1986
21. Stramentinoli G, Gualano M, Galli-Kienle M: Intestinal absorption of S-adenosyl-L-methionine. *J Pharmacol Exp Ther* 1979; 209:323-326
22. Carl GF, Crews EL, Carmichael SM, et al: Four enzymes of one carbon metabolism in the blood cells of schizophrenics. *Biol Psychiatry* 1978; 13:773-776
23. Bottiglieri T, Laundry M, Martin R, et al: S-Adenosylmethionine influences monoamine metabolism (letter). *Lancet* 1984; 2:224
24. Hirata F, Axelrod J: Phospholipid methylation and biological signal transmission. *Science* 1980; 209:1082-1089
25. Zawad JS, Brown FC: Beta-adrenergic coupled phospholipid methylation. *Biochem Pharmacol* 1984; 33:3799-3805
26. Zawad JS, Sulser F: S-Adenosyl-L-methionine modulates phosphatidylethanolamine methyltransferase response to isoproterenol in brain. *Eur J Pharmacol* 1986; 124:157-160
27. Carney MW: Neuropharmacology of S-adenosyl methionine. *Clin Neuropharmacol* 1986; 9:235-243

# Structured Interview Data on 102 Cases of Multiple Personality Disorder From Four Centers

Colin A. Ross, M.D., F.R.C.P.(C), Scott D. Miller, Ph.D., Pamela Reagor, Ph.D.,  
Lynda Bjornson, M.A., George A. Fraser, M.D., F.R.C.P.(C), and Geri Anderson, R.P.N.

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*Patients with multiple personality disorder (N=102) at four different centers were interviewed with the Dissociative Disorders Interview Schedule. The presenting characteristics of the patients at all four centers were very similar. The clinical profile that emerged included a history of childhood physical and/or sexual abuse in 97 (95.1%) of the cases. The subjects reported an average of 15.2 somatic symptoms, 6.4 Schneiderian symptoms, 10.2 secondary features of the disorder, 5.2 borderline personality disorder criteria, and 5.6 extra-sensory experiences; their average score on the Dissociative Experiences Scale was 41.4. The results indicate that multiple personality disorder has a stable, consistent set of features.*

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Multiple personality disorder was the subject of an almost entirely anecdotal literature until 1980 (1). Since then, several review papers (2-4) have attested to the increasing database for this disorder, which includes four large published series totaling 741 cases (5-8). However, there has not yet been a report of a study describing the phenomenology of multiple personality disorder in which a valid and reliable structured interview has been used by investigators at a number of different centers.

It was only recently that the first studies which used a valid and reliable self-report instrument for dissociation, the Dissociative Experiences Scale (9, 10), were published. Similarly, studies based on structured interview data for dissociative disorders began to enter the literature only in 1988 (11-17). These reports were based on information gathered with the Dissociative Disorders Interview Schedule (14, 17) and the Structured Clinical Interview for DSM-III-R Dissociative

Disorders (18), with which dissociative disorder diagnoses can also be made.

To determine the features of multiple personality disorder as it presents itself in patients at specialty clinics in North America, we used the Dissociative Experiences Scale and the Dissociative Disorders Interview Schedule to gather data on 102 cases of multiple personality disorder at four centers.

## METHOD

### Subjects

The subjects were 92 women and 10 men with clinical diagnoses of multiple personality disorder in four centers: Winnipeg, Canada (N=50), Utah (N=20), California (N=17), and Ottawa, Canada (N=15). The subjects in Winnipeg were 50 consecutively diagnosed patients assessed at a dissociative disorders clinic. In almost all cases, they were administered the Dissociative Experiences Scale and the Dissociative Disorders Interview Schedule by the research nurse before clinical assessment and before treatment. All but four of these subjects received their clinical diagnoses from the first author, a psychiatrist; the remaining four were given diagnoses by the research nurse (G.A.), who has extensive experience in the diagnosis and treatment of multiple personality disorder.

In Utah the subjects were volunteer subjects for a doctoral thesis. In California subjects were assessed with both instruments at the time of their clinical referral to a private outpatient facility, and clinical evaluation was carried out by a doctoral-level psychologist (P.R.) or a master's-level psychological assistant (L.B.). In Ottawa the subjects were interviewed with the two instruments specifically as part of the current study, and many were in treatment. All had been given clinical diagnoses by a psychiatrist.

All subjects gave signed consent. None of the authors had met the subjects from any of the other centers.

### Instruments

The Dissociative Experiences Scale is a 28-item self-report instrument with a test-retest reliability of 0.84

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Received June 14, 1989; revision received Oct. 25, 1989; accepted Nov. 8, 1989. From the Departments of Psychiatry, University of Manitoba and St. Boniface Hospital, Winnipeg; the Department of Psychiatry, University of Ottawa; Canyon Springs Hospital, Cathedral City, Calif.; and Heuler, Reagor and Associates, Orange, Calif. Address reprint requests to Dr. Ross, Department of Psychiatry, St. Boniface Hospital, 409 Tache Ave., Winnipeg, Manitoba R2H 2A6, Canada.

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and good clinical validity (9). It is a screening instrument for dissociative disorders, not a diagnostic instrument, with possible scores ranging from 0 to 100; two published studies (9, 10) have demonstrated that median scores on the scale differentiate patients with multiple personality disorder from those with other psychiatric disorders.

The Dissociative Disorders Interview Schedule is a structured interview that takes 30–45 minutes to administer to most subjects. It has an interrater reliability of 0.68, a sensitivity of 90%, and a specificity of 100% for the diagnosis of multiple personality disorder (14). In more than 400 administrations of this interview to adult patients and nonclinical subjects, the authors have not observed a false positive diagnosis of multiple personality disorder.

The Dissociative Disorders Interview Schedule is used to make *DSM-III-R* diagnoses of somatization disorder, major depressive episode, borderline personality disorder, and all the dissociative disorders. All 35 *DSM-III-R* symptoms of somatization disorder are inquired about. This schedule asks in detail about childhood physical and sexual abuse and a variety of features associated with multiple personality disorder, including 11 Schneiderian symptoms, 16 secondary features of multiple personality disorder, and 16 extrasensory experiences. The primary features of multiple personality disorder are the formal diagnostic criteria, while the secondary features are associated phenomena characteristic of the disorder.

Secondary features of multiple personality disorder include voices coming from inside one's head, the existence of another person inside the subject, another person taking control of one's body, voices talking (whether inside or outside one's head), extensive amnesia for childhood after age 5, referring to oneself as "we" or "us," blank spells or discrete periods of missing time, flashbacks, being told by others of unremembered events, feelings of unreality or depersonalization experiences, noticing objects missing from one's environment, coming out of a blank spell in unfamiliar surroundings and not knowing how one got there, strangers knowing the subject, objects present in the environment that cannot be accounted for, finding samples of different handwriting, and another person inside having a different name. Respondents are asked about the existence of other people inside them because this is frequently how they experience their alternate personalities; the question does not imply that the interviewer believes that there is more than one person inside the patient.

The 16 extrasensory experiences inquired about by the Dissociative Disorders Interview Schedule include mental telepathy, clairvoyance, telekinesis, contact with ghosts, spirits, or poltergeists, possession experiences, and knowledge of past lives, among others. The Schneiderian symptoms include several forms of auditory hallucination, passivity experiences in which thoughts, feelings, or actions are experienced as under the control of an outside force, thought broadcasting,

delusions, thought insertion and withdrawal, and hearing one's thoughts as if spoken out loud (19).

The Dissociative Disorders Interview Schedule and its scoring rules are available in two sources (14, 17).

### Procedure

Dissociative Disorders Interview Schedule interviews were conducted with all 102 subjects, and the forms were then sent to the coordinating center for computer entry and analysis. The subjects in Utah ( $N=20$ ) did not complete the Dissociative Experiences Scale.

Data were first analyzed to determine whether there were differences among subjects at the four centers. Statistical significance was set at  $p<0.05$ , and the Bonferroni correction for multiple comparisons was applied (20). Items were grouped into families for this purpose.

In comparing data at the four centers, chi-square tests were used for dichotomous data. For continuous data, the Kolmogorov-Smirnov statistic for normality was used to determine whether the variables were normally distributed. Since they were not, the Kruskal-Wallis test was used to determine significance for continuous data. Use of nonparametric statistics yielded the same results as parametric analysis.

Data from the four centers were then pooled and a descriptive analysis was carried out. Finally, a stepwise regression analysis was performed to determine which items in the Dissociative Disorders Interview Schedule best accounted for the variability in scores on the Dissociative Experiences Scale (Utah subjects excluded). Five items on the interview schedule were selected as predictor variables for regression analysis because they had been shown in previous research to best discriminate patients with multiple personality disorder from other diagnostic groups (12, 16). These items were somatic symptoms, Schneiderian symptoms, secondary features of multiple personality disorder, extrasensory experiences, and criteria for borderline personality disorder.

### RESULTS

Subjects at the four centers did not differ on any items in the Dissociative Disorders Interview Schedule, including demographic data, or overall scores on the Dissociative Experiences Scale, with two exceptions: the subjects in Winnipeg had fewer secondary features of multiple personality disorder, and they had experienced fewer types of sexual abuse than those in Utah. The subjects in Winnipeg had a mean $\pm$ SD of  $9.1\pm3.6$  secondary features of multiple personality disorder, whereas the mean for the Utah subjects was  $13.0\pm2.4$  ( $\chi^2=18.73$ ,  $df=3$ ,  $p<0.0003$ ). With the Bonferroni correction applied, the significance level for this item was  $p<0.003$ . The subjects in Winnipeg had experienced a mean $\pm$ SD of  $3.3\pm2.9$  different forms of sexual



TABLE 1. Abuse Histories of Multiple Personality Disorder Patients in Five Large Series

Type of Abuse	Putnam et al. (5) (N=100)		Ross et al. (6) (N=236)	Coons et al. (7) (N=50)		Schultz et al. (8) (N=355)	Present Study (N=102)	
	N	%		N	%		N	%
Sexual	83	83.0	79.2	34	68.0	86.0	92	90.2
Physical	75	75.0	74.9	30	60.0	82.0	84	82.4
Physical or sexual or both	—	—	88.5	48	96.0	—	97	95.1

abuse (14, 17), whereas the mean was  $6.7 \pm 3.5$  for the subjects in Utah ( $\chi^2=19.15$ ,  $df=3$ ,  $p<0.0003$ ). With the Bonferroni correction applied, the significance level for this item was  $p<0.004$ . The Dissociative Disorders Interview Schedule inquires about 12 different forms of sexual abuse, including fondling, fellatio, cunnilingus, intercourse, bestiality, and participation in the production of pornography.

When data from the four centers were pooled, a total of 102 cases of multiple personality disorder were available for descriptive analysis. Of the 102 individuals, 92 (90.2%) were female and 10 (9.8%) were male; 49.0% (N=50) had never been married, 31.4% (N=32) were married, 18.6% (N=19) were separated or divorced, and 0.9% (N=1) was widowed. The mean  $\pm$  SD number of children per subject was  $1.0 \pm 1.4$ . Forty-four (43.1%) of the subjects were employed.

As shown in table 1, 90.2% of the subjects reported a history of childhood sexual abuse, and 82.4% reported physical abuse. Altogether, 95.1% of the subjects had experienced one or both of these forms of childhood trauma.

Substance abuse was common. Of the 102 patients, 33.3% (N=34) had had a drinking problem at some time, 28.4% (N=29) had used street drugs extensively, 9.8% (N=10) had injected drugs intravenously, and 15.7% (N=16) had had treatment for drug or alcohol abuse. Altogether, 50% of the subjects endorsed one or more of the items concerning substance abuse.

There was evidence of extensive involvement with the mental health system. Altogether, 95.1% (N=97) of the subjects had received treatment for an emotional disorder, and 75.5% (N=77) knew what diagnoses they had been given in the past; 72.5% (N=74) had been given diagnoses of depression, 26.5% (N=27) mania, 26.5% (N=27) schizophrenia, 46.1% (N=47) anxiety disorder, and 35.3% (N=36) multiple personality disorder.

Of the 102 individuals with multiple personality disorder, 86.3% (N=88) had been prescribed psychotropic medication or ECT. This included 55.9% (N=57) who received antipsychotic medication, 72.5% (N=74) an antidepressant, 29.4% (N=30) lithium, and 16.7% (N=17) ECT. Ninety-four percent (N=96) of the subjects had received courses of psychotherapy of at least five sessions in duration for emotional, family, or psychological problems; 76.5% (N=78) of the sub-

jects said that they had received ineffective treatment at some time.

There was evidence of high levels of suicidal ideation and self-abusive behavior. Ninety-two percent (N=94) of the subjects had had recurrent thoughts of death, suicidal thoughts, or wishes to be dead or had attempted suicide; 56.9% (N=58) had taken an overdose; 40.2% (N=41) had slashed their wrists or other body areas; 23.5% (N=24) had inflicted cigarette burns or other self-injuries; 26.5% (N=27) had used a gun, knife, or other weapon to harm themselves; and 12.7% (N=13) had attempted to hang themselves.

The mean  $\pm$  SD number of types of self-abuse reported per subject was  $1.9 \pm 1.7$ . Of the 102 subjects, 28 (27.5%) had not attempted suicide, 25 had used one method of self-abuse, 15 had used two methods, 13 had used three methods, 10 had used four, eight had used five, and three had used six.

The mean numbers of symptoms per subject in several key sections of the Dissociative Disorders Interview Schedule are shown in table 2. The mean score on the Dissociative Experiences Scale is also shown in table 2; the median score was 43.8, and the range was 1.25–83.6. Table 3 shows the frequency with which subjects endorsed each of the 16 secondary features of multiple personality disorder inquired about in the Dissociative Disorders Interview Schedule. Of the 102 subjects, 95.1% (N=97) endorsed five or more of these secondary features.

The key symptom clusters were endorsed by the majority of the 102 subjects: 90.2% (N=92) endorsed three or more Schneiderian symptoms, 91.2% (N=93) endorsed two or more borderline personality disorder criteria, 92.2% (N=94) endorsed five or more somatic symptoms, and 89.2% (N=91) endorsed two or more extrasensory experiences.

Headache was reported by 90 subjects, and 37.8% (N=34) of these individuals stated that they had been given a diagnosis of migraine headache by a doctor. Ninety-two percent (N=94) of the subjects reported going into trances, 55.9% (N=57) had walked in their sleep, and 48.0% (N=49) had had imaginary companions as children.

A great many of these 102 patients with multiple personality disorder had other concurrent psychiatric diagnoses according to the Dissociative Disorders Interview Schedule. Ninety-three (91.2%) had diagnoses of major depressive disorder, 65 (63.7%) border-

**TABLE 2. Features Associated With Multiple Personality Disorder in 102 Patients**

Item	Mean	SD
Somatic symptoms	15.2	7.3
Schneiderian symptoms	6.4	2.8
Secondary features of multiple personality disorder	10.2	3.5
Borderline personality disorder criteria	5.2	2.3
Extrasensory experiences	5.6	3.3
Dissociative Experiences Scale score	41.4	20.0

line personality disorder, and 62 (60.8%) somatization disorder.

Table 4 shows the frequency distribution for endorsement of amnesia items, of which there are six, on the Dissociative Disorders Interview Schedule. These include the amnesia criterion from *DSM-III-R* somatization disorder, three secondary features of multiple personality disorder from those shown in table 3, criterion A for *DSM-III-R* psychogenic amnesia, and the fifth National Institute of Mental Health research criterion for multiple personality disorder, which specifies the existence of some type of amnesia or combination of types of amnesia among the different personalities. One hundred percent of the subjects endorsed at least one of the six amnesia criteria; 88.2% (N=90) endorsed three or more.

When a stepwise regression analysis was conducted with Dissociative Experiences Scale score as the criterion variable, only one predictor variable, secondary features of multiple personality disorder, entered the regression at  $p < 0.05$ . The corrected  $R^2$  value for secondary features of multiple personality disorder was 0.36 ( $\beta = 0.61$ ;  $p < 0.00001$ ).

## DISCUSSION

These findings provide the first data on multiple personality disorder from structured interviews conducted in several centers. Both of the instruments used in the study have demonstrated validity and reliability. Secondary features of multiple personality disorder revealed by the Dissociative Disorders Interview Schedule accounted for a large amount of the variability in scores on the Dissociative Experiences Scale ( $\beta = 0.61$ ). The experiences inquired about in the secondary features section of the Dissociative Disorders Interview Schedule are similar to subitems of the Dissociative Experiences Scale; the two instruments appear to tap the same domain.

There is now a series of published studies of multiple personality disorder that are cross-linked with each other and that together provide a strong case for consistency in the features of the disorder. As shown in table 1, the rates of childhood physical and sexual abuse for patients with multiple personality disorder in

**TABLE 3. Frequency of 16 Secondary Features of Multiple Personality Disorder in 102 Patients**

Item	Subjects	
	N	%
Another person existing inside	92	90.2
Voices talking	89	87.3
Voices coming from inside	84	82.4
Another person taking control	83	81.4
Amnesia for childhood	83	81.4
Referring to self as "we" or "us"	75	73.5
Person inside has a different name	72	70.6
Blank spells	69	67.7
Flashbacks	68	66.7
Being told by others of unremembered events	64	62.8
Feelings of unreality	58	56.9
Strangers know the patient	45	44.1
Noticing that objects are missing	43	42.2
Coming out of blank spell in a strange place	37	36.3
Objects are present that cannot be accounted for	32	31.4
Different handwriting styles	28	27.5

four large series (5–8) and the present study are in the same range: 60%–82% of the subjects had been physically abused, 68%–90% had been sexually abused, and over 88% had been victims of one or both forms of childhood trauma. These are conservative estimates of the rates of childhood abuse, because some of the respondents may have had amnesia for childhood trauma at the time of interview. An additional series of 70 subjects reported by Bliss (21) contained both confirmed and possible cases of multiple personality disorder, but the rates of abuse for the confirmed subgroup were not stated separately.

Ross et al. (6) showed that 236 subjects with multiple personality disorder were similar in many characteristics to those in 100 cases reported to Putnam et al. (5) with a different questionnaire. In addition, Ross et al. (10) showed that median scores on the Dissociative Experiences Scale differentiated patients with multiple personality disorder from those with other psychiatric disorders in much the same way that they did in the original development of the scale. It is important to emphasize that this scale is a screening, not a diagnostic, instrument and that high scores only suggest a dissociative disorder.

In another study, Ross et al. (22) compared 22 patients with multiple personality disorder in Winnipeg and 23 such patients in Ottawa to patients from the series of 236. Results showed that cases of multiple personality disorder in Winnipeg and Ottawa did not differ from each other, from cases reported by Canadian general psychiatrists, or from cases reported by American psychiatrists specializing in the disorder. These studies demonstrate that the disorder has a consistent, stable set of features and that the findings are consistent when different questionnaires are used.

Previous studies have shown that men and women with multiple personality disorder do not differ in a

**TABLE 4.** Frequency Distribution of Number of Amnesia Items Endorsed on Structured Interview for 102 Patients With Multiple Personality Disorder

Number of Items Endorsed	Number of Patients	Cumulative Percent
0	0	0.0
1	3	2.9
2	9	11.8
3	13	24.5
4	28	52.0
5	41	92.2
6	8	100.0

wide range of features, including number of alternate personalities (23). In addition, subjects with multiple personality disorder who have been hypnotized do not differ from those who have not been hypnotized on a large number of variables, including total number of personalities (24). The features of the disorder are consistent whether cases are diagnosed by psychiatrists or psychologists, in private clinics or at teaching hospitals.

Multiple personality disorder is linked to much higher rates of childhood trauma than any other psychiatric disorder; it appears to represent a dissociative strategy for coping with and surviving this abuse. Patients with this disorder have many symptoms, and the vast majority have one or more concurrent diagnoses, such as substance abuse, depression, somatization disorder, and borderline personality. Other common concurrent diagnoses not inquired about by the Dissociative Disorders Interview Schedule include panic disorder and eating disorders (17, 25). Patients with multiple personality disorder are probably the most self-destructive diagnostic group among psychiatric patients.

Despite its manifestation through many different symptoms, multiple personality disorder can be differentiated from other psychiatric disorders at high levels of significance on a large number of interview items (12). Most patients with multiple personality disorder have numerous somatic and Schneiderian symptoms (19), borderline criterion symptoms, extrasensory experiences, and high scores on the Dissociative Experiences Scale. Most report numerous secondary features of multiple personality disorder; these may be pathognomonic for the disorder when more than five are present in conjunction with the rest of the Dissociative Disorders Interview Schedule profile, especially childhood abuse. It is noteworthy that 70.6% of the multiple personality disorder subjects in the present study said that they had another person inside who had a different name. This appears to be a secondary feature, which is revealed to the clinician at the initial assessment in the majority of cases.

The proposed *DSM-IV* criteria for the disorder (see appendix 1) appear to yield very few, if any, false positive diagnoses in clinical subjects. One advantage of using the Dissociative Disorders Interview Schedule in clinical assessments is that a malingerer would have to be aware of the entire multiple personality disorder

profile to produce a convincing picture of the disorder on that structured interview.

As multiple personality disorder is more widely recognized and diagnosed, the risk of false positive diagnoses with the *DSM-III-R* criteria will increase. It is for this reason that more stringent criteria, including amnesia, are recommended for *DSM-IV*. These proposed criteria might result in false negative diagnoses for patients who do not have amnesia—it is possible that a form of multiple personality disorder without amnesia exists in the general population—but such individuals do not seem to present to clinicians for treatment with any frequency. Excluding such individuals as having false negative diagnoses is a more conservative diagnostic error than overincluding subjects with false positive diagnoses.

Although patients with multiple personality disorder currently spend an average of 6.8 years in the mental health system from first presentation to diagnosis (5, 6), their disorder can be diagnosed with good validity and reliability when a specific inquiry for its features is made. These features have differentiated multiple personality disorder from schizophrenia, panic disorder, eating disorder, complex partial seizures, and neurological disorders in several published studies (12, 13). As the present study and previous studies (5, 6) show, the patient with undiagnosed multiple personality disorder receives many different diagnoses and treatments during his or her 6.8 years in the mental health system before the correct diagnosis is made. Some of the previous diagnoses, such as major depressive episode, are correct concurrent diagnoses. Others, often including non-*DSM-III-R* entities such as “hysterical schizophrenia,” are diagnostic errors.

Once a systematic inquiry for multiple personality disorder is made part of the routine diagnostic assessment of all individuals presenting to mental health facilities, the disorder will no longer be thought to be rare. Because multiple personality disorder is often treatable with specific psychotherapy to the point of long-term remission (17, 25, 26), such an inquiry should be part of standard clinical practice. In addition, structured diagnostic interviews for use in epidemiological surveys should make specific inquiries for dissociative disorders. There is a sufficiently large active caseload of multiple personality disorder patients in North America for norms on multiple personality disorder items in research instruments to be derived. This study represents the first attempt to derive norms for a dissociative disorder by using a valid and reliable structured interview in several different centers.

#### REFERENCES

1. Greaves GB: Multiple personality disorder: 165 years after Mary Reynolds. *J Nerv Ment Dis* 1980; 168:577-596
2. Kluft RP: The treatment of multiple personality disorder (MPD): current concepts. *Directions in Psychiatry* 1985; 5(24): 1-10
3. Kluft RP: Making the diagnosis of multiple personality disorder (MPD). *Directions in Psychiatry* 1985; 5(23):1-10

4. Kluft RP: An update on multiple personality disorder. *Hosp Community Psychiatry* 1987; 38:363-373
5. Putnam FW, Guroff JJ, Silberman EK, et al: The clinical phenomenology of multiple personality disorder: review of 100 recent cases. *J Clin Psychiatry* 1986; 47:285-293
6. Ross CA, Norton GR, Wozney K: Multiple personality disorder: an analysis of 236 cases. *Can J Psychiatry* 1989; 34:413-418
7. Coons PM, Bowman ES, Milstein V: Multiple personality disorder: a clinical investigation of 50 cases. *J Nerv Ment Dis* 1988; 176:519-527
8. Schultz R, Braun BG, Kluft RP: Multiple personality disorder: phenomenology of selected variables in comparison to major depression. *Dissociation* 1989; 2(1):45-51
9. Bernstein EM, Putnam FW: Development, reliability, and validity of a dissociation scale. *J Nerv Ment Dis* 1986; 174:727-735
10. Ross CA, Norton GR, Anderson G: The Dissociative Experiences Scale: a replication study. *Dissociation* 1988; 1(2):21-22
11. Ross CA, Anderson G: Phenomenological overlap of multiple personality disorder and obsessive-compulsive disorder. *J Nerv Ment Dis* 1988; 176:295-299
12. Ross CA, Heber S, Norton GR, et al: Differences between multiple personality disorder and other diagnostic groups on structured interview. *J Nerv Ment Dis* 1989; 177:487-491
13. Ross CA, Anderson G, Heber S, et al: Differentiating multiple personality disorder and complex partial seizures. *Gen Hosp Psychiatry* 1989; 11:54-58
14. Ross CA, Heber S, Norton GR, et al: The Dissociative Disorders Interview Schedule: a structured interview. *Dissociation* 1989; 2(3):169-189
15. Ross CA, Anderson G, Heber S, et al: Dissociation and abuse in multiple personality patients, prostitutes, and exotic dancers. *Hosp Community Psychiatry* (in press)
16. Ross CA, Heber S, Norton GR, et al: Somatic symptoms in multiple personality disorder. *Psychosomatics* 1989; 30:154-160
17. Ross CA: *Multiple Personality Disorder: Diagnosis, Clinical Features, and Treatment*. New York, John Wiley & Sons, 1989
18. Steinberg M, Rounsaville B, Cicchetti DV: The Structured Clinical Interview for *DSM-III-R* Dissociative Disorders: a preliminary report on a new diagnostic instrument. *Am J Psychiatry* 1990; 147:76-82
19. Kluft RP: First-rank symptoms as a diagnostic clue to multiple personality disorder. *Am J Psychiatry* 1987; 144:293-298
20. Grove WM, Andreasen NC: Simultaneous tests of many hypotheses in exploratory research. *J Nerv Ment Dis* 1982; 170:3-8
21. Bliss EL: A symptom profile of patients with multiple personalities, including MMPI results. *J Nerv Ment Dis* 1984; 172:197-202
22. Ross CA, Norton GR, Fraser G: Evidence against the iatrogenesis of multiple personality disorder. *Dissociation* 1989; 2(2):61-65
23. Ross CA, Norton GR: Differences between men and women with multiple personality disorder. *Hosp Community Psychiatry* 1989; 40:186-188
24. Ross CA, Norton GR: Effects of hypnosis on the features of multiple personality disorder. *Am J Clin Hypn* 1989; 32:99-106
25. Putnam FW: *Diagnosis and Treatment of Multiple Personality Disorder*. New York, Guilford Press, 1989
26. Kluft RP: Treatment of multiple personality disorder. *Psychiatr Clin North Am* 1984; 7(1):9-29

#### APPENDIX 1. Proposed *DSM-IV* Diagnostic Criteria for Multiple Personality Disorder

- A. The existence within the individual of two or more distinct personalities or personality states (each with its own relatively enduring pattern of perceiving, relating to, and thinking about the environment and self)
- B. At least two of these personalities or personality states recurrently take full control of the person's behavior
- C. The presence of at least one of the following:
  1. Blank spells or periods of missing time
  2. Coming out of a blank spell in unfamiliar surroundings, unsure of how he or she got there
  3. Extensive amnesia for childhood after age 5
  4. Evidence of some other form of amnesia between personalities (i.e., one-way amnesia, mutual amnesia)



# Suicide and Schizophrenia: Data From a Prospective Community Treatment Study

Lawrence J. Cohen, Ph.D., Mary Ann Test, Ph.D., and Roger L. Brown, Ph.D.

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*This article reports the analysis of prospectively gathered data on eight young adults who committed suicide during an ongoing longitudinal study of long-term treatment of schizophrenia in the community. Young adult men with an early onset of psychiatric illness were identified as a high-risk subgroup. At the time of admission to the study, the subjects who eventually committed suicide reported significantly more distress and tended to be less satisfied with their lives than the other subjects. Specifically, baseline measures of self-reported subjective distress were consistently predictive of later suicide, whereas interviewer-rated measures and postbaseline assessments were not.*

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(Am J Psychiatry 1990; 147:602-607)

Suicide is the most devastating possible outcome of a schizophrenic illness. In addition to the finality for the patients, suicide has an intense and long-lasting impact on families, other patients, and professional staff. Furthermore, it is becoming increasingly clear that suicide among schizophrenic persons is not an isolated phenomenon. It is the leading cause of premature death in this population (1); recent studies have estimated a 10% incidence of suicide in the first 10 years of the illness and a 15% lifetime incidence (2).

While innovative systems, especially those providing comprehensive community-based care, have made great strides in the medical and psychosocial treatment of schizophrenia, these advances have not eradicated suicide. Training in Community Living, for example—a model of community-based treatment for seriously mentally ill adults—has been shown to be effective in keeping patients out of the hospital and in the community, in symptom reduction, and in helping patients

with employment, independent living, and social functioning (3), yet findings from an in-progress study of this model with young adult patients suggest that suicide continues to be a considerable problem.

In previous studies of suicide among schizophrenic persons, the most consistent findings have involved gender differences and the period of greatest risk. Johns et al. (4) reported that 75%–90% of suicides in this population are committed by men and that suicide is most common during the first 10 years of the illness. Studies of older patients, however, have revealed that there are suicides throughout the life span and at all stages of illness (5).

Various symptoms, including feelings of inner disintegration and persecution (6) and severity of hallucinations and delusions (4), have been found to predict suicide among persons with schizophrenia. Because of the high base rates of these symptoms, such observations are not very helpful in identifying patients at highest risk. Certain symptoms of depression, especially hopelessness, tend to be more powerful discriminators (4, 7). Other variables that have been tentatively suggested as predictors of suicide among schizophrenic persons include loss of family support (8), poor social and sexual functioning (2), negative attitudes toward treatment (9), better premorbid functioning (10), and loss of access to care (S. Mestrovic and J. Cook, unpublished paper, 1982).

Our report is based on an intensive study of the individuals who have committed suicide during an in-progress longitudinal study of long-term treatment of schizophrenia in the community (11). Unlike most other studies of suicide and schizophrenia, this analysis was based on a wealth of prospectively gathered data, including repeated standardized measures of self-reported and interviewer-rated symptoms. The extent of the data available for review, combined with the demonstrated effectiveness of the treatment system, allows for an increased level of understanding of suicide by patients with schizophrenia and related disorders.

## METHOD

The subjects of this analysis were admitted to the ongoing study from 1978 to 1986 according to the

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Revised version of a paper presented at the 142nd annual meeting of the American Psychiatric Association, San Francisco, May 6–11, 1989. Received March 9, 1989; revision received Sept. 12, 1989; accepted Nov. 8, 1989. From the Department of Psychiatry, the School of Social Work, and the Department of Family Medicine, University of Wisconsin-Madison. Address reprint requests to Dr. Test, School of Social Work, 425 Henry Mall, Madison, WI 53706.

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following criteria: residence in Dane County, Wisconsin; age, 18–30 years; diagnosis of schizophrenia or schizoaffective disorder according to the Research Diagnostic Criteria (RDC) (12) or of schizotypal personality disorder according to *DSM-III*; less than 1 year of total prior time spent in psychiatric or penal institutions; and absence of a primary diagnosis of mental retardation, organic brain syndrome, or alcoholism.

Patients in the study (N=122) received treatment from the Training in Community Living program (N=75) or the usual system of care in Dane County (N=47). They were randomly assigned to one of the two treatment conditions in a ratio of 60:40, respectively, to ensure an adequate number in the community living condition for additional within-group analyses. Both treatment systems are well-known progressive models of community care for the seriously mentally ill (13). For a detailed description of the Training in Community Living program, the design of the long-term study, and the characteristics of the sample as a whole, see Test et al. (11).

As part of the assessment procedures of the in-progress long-term study, independent research staff members interview all subjects at the time of admission to the study and approximately every 6 months thereafter for a period of 5–12 years. The interviews cover a range of areas including demographics, preadmission history, and social and sexual functioning. The assessment protocols also include a standardized measure of self-reported symptoms, the SCL-90-R (14); an interviewer-rated measure of symptoms, the Brief Psychiatric Rating Scale (BPRS) (15); and a self-report measure of satisfaction with various aspects of life (3).

## RESULTS

### *Suicide Rate by Treatment Condition and Gender*

The sample of 122 subjects in the longitudinal study consisted of 82 men (67.2%) and 40 women (32.8%). At the time of the substudy on suicide, all surviving subjects had been treated and followed for at least 4 years; the average was 8.26 years. There had been 10 deaths during this period. Eight were judged to be definite suicides, one was seen as a possible suicide, and one was a homicide. The determination of definite suicide was made if the treatment staff considered the death an unambiguous instance of a patient's intentionally taking his or her own life. The possible suicide, a death by motor vehicle, was judged to be an accident by legal authorities, but the staff continued to have doubts about the patient's intentions.

The eight definite suicides represent a rate of 6.6% of the sample, or an average of 0.8% per year. This figure is only slightly lower than the commonly cited rate of 1.0% per year during the early years of schizophrenic illness, despite the fact that the patients in the

current study were receiving some of the most comprehensive and continuous care available in the country. In addition, the rate of definite suicides did not differ according to treatment condition; the incidence for this period was five of 75 (6.7%) in the community living group and three of 47 (6.4%) in the Dane County system group. This difference was not statistically significant ( $\chi^2=0.10$ ,  $df=1$ ,  $p=0.75$ , with Yates' correction). The one possible suicide had been a patient in the Training in Community Living group.

All of the patients who had definitely committed suicide were male; the possible suicide victim was a woman. Perhaps because of limitations in sample size, this gender difference was not statistically significant at the  $p<0.05$  level by chi-square test. However, the data suggest that men are a clearly identifiable high-risk subgroup of young adults with schizophrenia or related disorders. The analyses that follow include only the patients who definitely committed suicide. Since these were all male, the other male subjects in the study (N=74) were used as a comparison group.

### *Demographic and History Variables*

Table 1 presents data on several age characteristics for the suicide sample and for the male subjects who did not commit suicide. The subjects who committed suicide were significantly younger than the others when they had their first contact with the mental health care system and when they were admitted to the study. The difference between the two groups in age at first psychiatric hospitalization (for those who were hospitalized) approached significance. At the time of their deaths, the subjects who committed suicide ranged in age from 20 to 27 years ( $\text{mean} \pm \text{SD} = 22.9 \pm 2.3$  years). They had been treated and followed in the study for a  $\text{mean} \pm \text{SD}$  of  $2.9 \pm 1.9$  years. The subjects who committed suicide, then, represented a group with very early onset of illness, and the suicides tended to occur early in the course of the illness.

No significant differences between the suicide and nonsuicide groups were found on the variables of marital status, parental divorce, prior arrests, prior employment, family history of psychiatric hospitalization, source of primary financial support, highest educational level, history of being held back in school or placed in special education classes, or self-reported substance use during the 6 months preceding admission to the study. Caution must be exercised in accepting a conclusion of no difference, however, because of the low statistical power related to the small sample size.

All of the eight men who committed suicide were Caucasian, and at the time of admission to the study, none had ever been married (one subsequently married). Six of the eight had a high school diploma or a General Equivalency Diploma.

TABLE 1. Age Characteristics of Eight Male Schizophrenic Patients Who Committed Suicide and 74 Who Did Not

Characteristic	Suicide Group			Nonsuicide Group			Significance (Mann-Whitney U test)
	N	Mean	SD	N	Mean	SD	
Age at admission to study (years)	8	19.9	2.17	74	22.9	3.36	$z = -2.53, p < 0.05$
Age at first contact with mental health system (years)	8	16.5	1.85	72	19.3	4.66	$z = -2.69, p < 0.001$
Age at first psychiatric hospital admission (years)	7	18.6	1.40	55	20.6	3.14	$z = -1.66, p < 0.10$

### *Clinical Characteristics at Time of Entry Into the Study*

All of the patients in the long-term study met the criteria for one of the three admission diagnoses according to the screening staff. An independent psychiatric resident trained in the use of the RDC then made the research diagnosis. Seven of the eight patients who definitely committed suicide were given diagnoses of schizophrenia; the other was given the diagnosis of schizoaffective disorder. The research diagnoses of the suicide patients did not differ significantly from those of the male nonsuicide comparison group. However, chart reviews of the suicide group revealed that, in addition to their high frequency of clinical diagnoses of schizophrenia, six of the eight patients had at some time (either before or after entry into the study) received diagnoses of affective or schizoaffective disorders. This observation suggests that patients at highest risk for suicide may present with mixed, ambiguous, or changing patterns of signs and symptoms.

Table 2 presents data for the suicide and nonsuicide male patients, at the time of their entry into the study, on symptom and functioning variables measured during the initial (baseline) research assessment. Because of asymmetry in the data, the Mann-Whitney U test of median differences was used; no allowances were made for multiple comparisons.

Because of inconsistencies in previous reports, the three standardized measures (the SCL-90-R, the BPRS, and the life satisfaction scale) were factor analyzed to provide specific results for the sample in the ongoing study (R.L. Brown and M.A. Test, unpublished manuscripts, 1986, 1988). The suicide group reported significantly more symptoms and distress than the nonsuicide group on the hopelessness, hostility, depression, obsessive-compulsive, and paranoid ideation subscales of the SCL-90-R. Differences on the other subscales were in the same direction but were not statistically significant.

On the BPRS, an interviewer-rated measure, the suicide group was not rated as significantly more symptomatic than the nonsuicide group. On the life satisfaction scale, the subjects who later committed suicide generally reported less satisfaction at baseline than the nonsuicide comparison group, although none of the differences on the subscales was statistically signifi-

cant. The differences approached significance for social relationships and enjoyment of life.

Another indicator of subjective distress was number of days that the person felt lonely and hopeless. As table 2 shows, the patients who later committed suicide reported more days feeling lonely and more days feeling hopeless, although these differences did not reach significance.

In contrast to this pattern of difference, data relevant to social relationships suggest that the suicide subjects may have been no more socially isolated at baseline than the average male nonsuicide subject. Specifically, as seen in table 2, there were no significant differences in number of friends and acquaintances or in number of days patients did not contact anyone when they felt lonely or hopeless. In addition, there were no significant differences in the percentages of suicide and nonsuicide subjects who had at least one date, kissed someone, or had sex during the previous month. It should be noted, however, that these types of social and sexual interactions were rare for both groups.

As a whole, this sample of young adults with schizophrenic diagnoses had a high level of substance use (16), but the results did not suggest greater use by the suicide group either at the time of admission or in their preadmission histories. For instance, at the time of admission, 35 (47.3%) of the 74 male nonsuicide group but only one (14.3%) of the seven eventual suicide patients with data on this variable reported that they were using alcohol, marijuana, and/or a street drug at least several times per week ( $\chi^2 = 1.64, df = 1, p > 0.05$ , with Yates' correction). Reviews of clinical records supported these data by revealing that the majority of the patients who eventually committed suicide were minimal users of or abstainers from alcohol or street drugs.

### *Clinical Characteristics Over Time*

The measures of symptoms, distress, and social relationships reported in the previous section were repeated at 6-month intervals. The suicide and nonsuicide groups were compared at 6, 12, 18, and 24 months, the only times for which comparison data were available at the time of this writing. Because of shrinking sample sizes and asymmetrical data, an exploratory analytical procedure was used for group comparisons. This procedure establishes an estimated

TABLE 2. Baseline Symptom and Functioning Scores of Eight Male Schizophrenic Patients Who Committed Suicide and 74 Who Did Not

Measure	Suicide Group		Nonsuicide Group		Significance (Mann-Whitney U test)
	N	Median	N	Median	
SCL-90-R score <sup>a</sup>					
Hopelessness	8	6.30	69	2.96	$z=3.27, p<0.05$
Hostility	8	3.53	69	1.63	$z=2.09, p<0.05$
Somatization	8	1.97	69	1.76	n.s.
Depression	8	5.89	69	3.52	$z=2.21, p<0.05$
Paranoid ideation	8	4.51	69	2.71	$z=2.64, p<0.05$
Phobic anxiety	8	4.26	69	2.64	n.s.
Anxiety	8	3.89	69	2.37	n.s.
Obsessive-compulsive	8	3.73	69	2.23	$z=2.50, p<0.05$
BPRS score <sup>a</sup>					
Psychoticism	8	1.48	73	1.93	n.s.
Withdrawal	8	1.90	73	1.34	n.s.
Hostile/suspicious	8	1.74	73	1.48	n.s.
Anxiety/depression	8	2.66	73	2.20	n.s.
Activation	8	0.41	73	0.82	$z=-1.68, p<0.10$
Life satisfaction scale score <sup>a,b</sup>					
Patient problems	8	0.82	74	0.85	n.s.
Contact with opposite sex	8	2.68	74	2.70	n.s.
Relationships	8	1.29	74	1.84	$z=-1.91, p<0.06$
Living space	8	1.88	74	2.18	n.s.
Leisure activities	8	1.97	74	2.24	n.s.
Enjoyment of life	8	0.86	74	1.60	$z=-1.68, p<0.10$
Social activities	8	0.96	74	1.16	n.s.
Lonely and hopeless feelings					
Days feeling lonely in past week	8	5.5	71	2.0	n.s.
Days feeling hopeless in past 2 weeks	8	5.0	69	1.0	n.s.
Social relationships					
Number of friends	8	3.5	74	3.0	n.s.
Number of acquaintances	8	2.5	73	1.0	n.s.
Days feeling lonely and did not contact a friend	7	0.0	44	1.0	n.s.
Days feeling hopeless and did not contact a friend	7	1.0	40	1.0	n.s.

<sup>a</sup>Weighted factor regression scores.<sup>b</sup>Higher score indicates greater life satisfaction.

95% confidence interval around group median values, with nonoverlapping intervals indicating a median group difference significant at approximately the 5% alpha error level (17).

In contrast to the pattern of differences at baseline, the median scores of the two groups at these later time points were strikingly similar. The suicide group did not score significantly worse than the nonsuicide group on any measure at any of the postbaseline periods. While the suicide group declined sharply in level of distress after baseline, the nonsuicide group maintained a relatively stable profile of distress and symptoms over time. In one isolated postbaseline comparison, the suicide group actually reported significantly less distress than the comparison group, but this finding was not part of a consistent pattern across measures. The initial decline in distress by the suicide group was not due simply to attrition of extreme cases, since an analysis using only cases with complete data provided the same pattern of results.

The varying lengths of time that subjects spent in the study before they committed suicide and the 6-month gap between interviews make it impossible to examine

directly whether there was a rise in subjective or interviewer-rated distress immediately before the suicides. For the subjects who were last interviewed shortly before their deaths, however, the data tentatively suggest that distress does increase considerably during this period, especially in the areas of hopelessness and depression. Finally, in the area of substance abuse, there continued to be no significant differences between the suicide and nonsuicide groups in self-reported frequency of use; differences that were present were in the direction of less use by the suicide group. Chart reviews and interviews with staff members also failed to implicate substance abuse as a strong contributing factor in any of the suicides.

## DISCUSSION

The findings of this study are consistent with the literature in identifying a subgroup of persons at extreme risk for suicide, namely young adult men with schizophrenia or schizophrenia-related disorders. The current investigation indicates that this group remains



at serious risk even when treated in "model" community programs. The early age at entry into the psychiatric service system of the group that eventually committed suicide, coupled with a pattern of ambiguous or complex diagnostic issues, raises the possibility that this group constitutes a particular subtype of schizophrenic patient. The increased risk might be biologically determined or be due to the secondary effects of early experiences of symptoms and stigma, or some combination of the two.

The most striking findings of the study involve the high levels of subjective distress reported by the suicide group at the time they entered the study. Even though they were a small sample, this group's distress was significantly higher than that of the nonsuicide group, although the baseline assessments were made an average of 2.9 years before the suicides. This finding of high baseline distress is consistent with Beck et al.'s report (18) that patients who eventually committed suicide had significantly higher hopelessness scores than those who did not when they were assessed during hospitalization several years before their deaths.

The current study extends Beck et al.'s results by showing that the suicide group scored high not only on a measure of hopelessness but also on a range of other self-reported symptom areas. This pattern suggests a pervasive experience of subjective distress for these patients, extending to feelings of loneliness and dissatisfaction with social relationships. It is important to note that the patients who later committed suicide reported being more lonely and dissatisfied, but they may in fact have been no more isolated than the others in terms of number of social supports and contact with these supports. A possible explanation for this paradox may be found in Beck's theory (19) that persons at high risk for suicide have a negative cognitive set and thus may experience more distress and less hope than others under the same circumstances.

Beck et al. (18) theorized that hopelessness experienced by the presuicidal patient is not a "steady state" but is an underlying schema that becomes salient during a stressful period such as acute symptom exacerbation. Our multiple assessments over time provide support for this theory. We found that the suicide and nonsuicide groups were remarkably similar at post-baseline assessment periods because of improvements in the suicide group after the baseline interview. The marked differences occurred only at baseline, a time of acute psychotic symptoms for most patients in the study.

Beck et al. hypothesized further from their cross-sectional study that the hopelessness schema is reactivated at later times of stress, most notably immediately before the actual suicide. As noted above, our data do not provide a good test of this hypothesis, but our exploratory findings are consistent with it. Thus, while distress is not stable over time, elevation of the level of distress at one point might predict later elevations, thereby predicting a greater risk of suicide over the long term.

Taking this analysis one step further, in the current sample, the clustering of the suicides among men in their early twenties may have been due to an interaction between underlying hopelessness and the demands of this developmental period. This period is critical because psychiatric symptoms have a strong tendency to interfere with the developmental priorities of young adulthood, namely identity formation, intimacy, and work (20).

The risk of suicide may be especially high for men because schizophrenic symptoms tend to be more severe for men than for women (21) and because young adult men in our society often have special difficulties negotiating a balance between external demands and internal impulses. Similarly, early onset may be associated with higher suicide risk because symptoms and poor functioning during the teen years can lead to the development of an underlying schema of hopelessness, which then becomes prominent during periods of psychosis or other acute distress.

## CONCLUSIONS

This examination of a small but well-documented sample of suicides among persons with schizophrenia or related disorders found that young men with an early onset of illness were at highest risk and that early signs of intense distress were related to later suicide, despite marked improvement in the interim. These observations were made possible by the multiple repeated measures design, the long-term follow-along period, and the model treatment setting of the study. Most importantly, baseline measures of *self-reported* subjective distress and dissatisfaction with life were consistently predictive of later suicide, while more objective interviewer-rated measures were not.

In addition to the contributions to theory that we have discussed, these findings have important implications for overcoming the many obstacles to predicting suicide risk and preventing suicide. If replicated in other samples and settings, the data provide for the identification of a subgroup at greater risk, underline the need for greater sensitivity to self-reported distress, and demonstrate the clinical importance of hopelessness, loneliness, and dissatisfaction with life. Clinical observations of psychotic symptoms and bizarre behavior can deflect attention from suicidal intent or suicidal risk unless careful attention is paid to self-reported distress and subjective experiences of hopelessness. Similarly, improvements in symptoms or functioning can obscure the underlying risk for individuals who are prone to suicide during periods of stress or acute illness.

In general, suicide is a difficult topic to address clinically because of the anxiety it engenders. Hopelessness is an especially difficult symptom because of the difficulty of responding empathically to it and because of a pervasive assumption that the hopelessness of schizophrenic persons is realistic and therefore not a proper

target of treatment. Cognitive therapy directly addressing hopeless and suicidal cognitions has seldom been applied to patients with schizophrenic disorders (22). Overcoming the obstacles to effective prevention of suicide requires a systematic approach to assessment, monitoring, and intervention and an attitude of non-defensiveness, optimism, and hope.

## REFERENCES

1. Allebeck P, Wistedt B: Mortality in schizophrenia. *Arch Gen Psychiatry* 1986; 43:650-653
2. Nyman AK, Jonsson H: Patterns of self-destructive behavior in schizophrenia. *Acta Psychiatr Scand* 1986; 73:252-262
3. Stein LI, Test MA: An alternative to mental hospital treatment, I: conceptual model, treatment program, and clinical evaluation. *Arch Gen Psychiatry* 1980; 37:409-412
4. Johns CA, Stanley M, Stanley B: Suicide in schizophrenia. *Ann NY Acad Sci* 1986; 487:294-300
5. Yarden P: Observations on suicide in chronic schizophrenics. *Compr Psychiatry* 1974; 15:325-333
6. Warnes H: Suicide in schizophrenics. *Dis Nerv Syst* 1968; 29(suppl 5):35-42
7. Becker RE: Depression in schizophrenia. *Hosp Community Psychiatry* 1988; 39:1269-1275
8. Drake RE, Gates C, Cotton PG: Suicide among schizophrenics: a comparison of attempters and completed suicides. *Br J Psychiatry* 1986; 149:784-787
9. Virkkunen M: Attitude to treatment before suicide in schizophrenia and paranoid psychoses. *Br J Psychiatry* 1976; 128:47-49
10. Farberow NL, Shneidman ES, Neuringer C: Case history and hospitalization factors in suicides of neuropsychiatric hospital patients. *J Nerv Ment Dis* 1966; 142:32-44
11. Test MA, Knoedler WH, Allness DJ, et al: Characteristics of young adults with schizophrenic disorders treated in the community. *Hosp Community Psychiatry* 1985; 36:853-858
12. Spitzer RL, Endicott J, Robbins E: Research Diagnostic Criteria: rationale and reliability. *Arch Gen Psychiatry* 1978; 35:773-782
13. Stein LI, Test MA (eds): *The Training in Community Living Model: A Decade of Experience: New Directions for Mental Health Services* 26. San Francisco, Jossey-Bass, 1985
14. Derogatis LR: SCL-90-R: Administration, Scoring, and Procedures Manual, II. Towson, Md, Clinical Psychometric Research, 1983
15. Overall JE, Gorham DR: The Brief Psychiatric Rating Scale. *Psychol Rep* 1962; 10:799-812
16. Test MA, Wallisch LS, Allness DJ, et al: Substance abuse in young adults with schizophrenic disorders. *Schizophr Bull* 1989; 15:465-476
17. Velleman PF, Hoaglin DC: *Applications, Basics and Computing of Exploratory Data Analysis*. Belmont, Calif, Wadsworth Press, 1981
18. Beck AT, Steer RA, Kovacs M, et al: Hopelessness and eventual suicide: a 10-year prospective study of patients hospitalized with suicidal ideation. *Am J Psychiatry* 1985; 142:559-563
19. Beck AT: *Depression: Causes and Treatment*. Philadelphia, University of Pennsylvania Press, 1972
20. Erikson E: *Youth and Crisis*. New York, WW Norton, 1968
21. Test MA, Berlin SB: Issues of special concern to mentally ill women. *Professional Psychol* 1981; 12:136-145
22. Falloon IRH, Boyd JL, McGill CW: *Family Care of Schizophrenia: A Problem-Solving Approach to the Treatment of Mental Illness*. New York, Guilford Press, 1984

# Depressive Episodes and Dysphoria Resulting From Conjugal Bereavement in a Prospective Community Sample

Martha Livingston Bruce, Ph.D., M.P.H., Kathleen Kim, M.D., M.P.H.,  
Philip J. Leaf, Ph.D., and Selby Jacobs, M.D., M.P.H.

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*Using three waves of interviews from the New Haven Epidemiologic Catchment Area Program, the authors contrast the extent and nature of depressive episodes and dysphoria between newly bereaved (N=39) and married (N=1,047) respondents age 45 and older. Bereavement greatly increased the risk of both conditions. This observation did not appear to be an artifact because psychosocial risk factors were similar for the bereaved and married groups. Bereavement increased the risk for a depressive episode more among respondents who reported no prior dysphoria than among those who did. Among those meeting criteria for depression, the bereaved reported symptoms similar to those of the married group except for significantly fewer reports of guilt.*

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Every year, over 800,000 men and women in the United States experience the death of their spouse (1). Conjugal bereavement is considered one of the most stressful events of adulthood. The likelihood of depressive symptoms after the loss of a spouse has been well documented (2); indeed, depressive symptoms are generally considered a normal expression of grief. However, the amount and nature of these symptoms vary considerably (1-4). Even when the full syndrome of a major depressive episode is associated with bereavement, it usually is not considered a mental disorder according to *DSM-III-R*. Further, no clear consensus exists as to how to distinguish pathological grief from normal bereavement (2).

The ability to differentiate severe from nonsevere

reactions, to estimate the prevalence of these reactions among the newly bereaved, and to identify risk factors for these reactions has been limited by methodological problems in previous bereavement studies. Few of these studies have interviewed representative samples of the newly bereaved (3, 5). Since most studies are retrospective, they do not have prebereavement assessments of mental health status and cannot examine the extent to which prior psychiatric history contributes to a person's vulnerability to depression. In addition, the measures of depressive symptoms have varied across studies, and few studies have used standardized instruments to assess psychiatric status.

This study attempted to clarify the variation in grief reactions among the newly bereaved by using longitudinal data from the New Haven Epidemiologic Catchment Area Program's study of white respondents, age 45 and older, without a history of depression. Using the subsample of respondents age 45 and older who were married at the beginning of the study, we 1) identified those respondents who were bereaved during the 1-year study period (the "newly" bereaved), 2) compared 1-year prevalence rates of *DSM-III*-defined dysphoria and depressive episodes, as measured by the Diagnostic Interview Schedule, for the newly bereaved and their married counterparts, 3) tested whether a number of sociodemographic and psychiatric factors affect the likelihood of these outcomes, 4) estimated the duration of these episodes, and 5) compared the symptoms of depressive episodes among the bereaved and the nonbereaved.

## METHOD

Data for these analyses were drawn from the three waves of interviews of the New Haven Epidemiologic Catchment Area sample. Beginning in July 1980, interviews were obtained from a multistage probability sample of 3,058 adults age 18 years and older and an additional oversample of 1,976 elderly respondents age 65 and older who were living in the 13-town region (adult population of approximately 300,000). The total of 5,034 interviews represents an overall response rate of 77% for the first wave of the survey. The data collection methods used in the New Haven

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TABLE 1. Risk of Developing Dysphoria and Depression Within the Past Year for 39 Bereaved Subjects and 1,047 Married Subjects

Disorder	Prevalence				Odds Ratio (bereaved versus married)					
	Bereaved (N=39)		Married (N=1,047)		Unadjusted		Adjusted for Sex, Age, and Household Size		Adjusted for Sex, Age, Household Size, and Past Dysphoria	
	N	%	N	%	Ratio	95% Confidence Interval	Ratio	95% Confidence Interval	Ratio	95% Confidence Interval
Dysphoria	24	61.5	65	6.2	24.3 <sup>a</sup>	12.1–48.9	21.8	10.2–46.5	31.5 <sup>b</sup>	13.9–71.5
Depression	12	30.8	33	3.2	13.5 <sup>c</sup>	6.2–29.7	12.1	5.1–28.5	21.8 <sup>d</sup>	8.2–58.0

<sup>a</sup> $\chi^2=81.49$ ,  $df=1$ ,  $p<0.001$ .<sup>b</sup> $\chi^2=72.30$ ,  $df=1$ ,  $p<0.001$ .<sup>c</sup> $\chi^2=45.06$ ,  $df=1$ ,  $p<0.001$ .<sup>d</sup> $\chi^2=39.09$ ,  $df=1$ ,  $p<0.001$ .

Epidemiologic Catchment Area Program have been described in greater detail elsewhere (6, 7).

Respondents were reinterviewed twice at 6-month intervals. We defined newly bereaved respondents as those whose spouse died during the year between the first and third interviews. Since there were so few respondents who were widowed in younger age groups, we limited our analyses to respondents who were age 45 and older and married at the first interview. Among the 1,658 respondents in this group, 62 had died by the end of the study, 410 had dropped out of the study, and six were separated or divorced from their spouses. These analyses examine the remaining 1,180 respondents. The deceased were more likely to be men ( $\chi^2=13.14$ ,  $df=1$ ,  $p<0.001$ ), older ( $t=6.08$  [unequal variance],  $df=69.2$ ,  $p<0.001$ ), and from smaller households ( $\chi^2=7.82$ ,  $df=2$ ,  $p<0.05$ ) and to have a history of depressive episodes ( $\chi^2=3.95$ ,  $df=1$ ,  $p<0.05$ ) than those remaining in the study; these findings are consistent with the mortality analyses of all older members of the New Haven Epidemiologic Catchment Area Program (8). The 410 respondents who dropped out of the study did not differ statistically in sex, mean age, race, household size, or history of depressive episodes from those respondents who stayed in the study.

Psychiatric status was assessed by the Diagnostic Interview Schedule (DIS), a semistructured interview administered by lay interviewers (9). The DIS assesses the presence, duration, and severity of symptoms and excludes symptoms due to physical illness or medication use. Computer algorithms use the data from the DIS to generate psychiatric diagnoses consistent with *DSM-III*. Using recency probes, we found that past history indicated that respondents met criteria for a disorder during some point in their lifetime. "Recent prevalence" refers to respondents meeting criteria at any time during the year between the first and last interviews.

This report compares 1-year prevalence rates of dysphoria and depressive episode between the newly bereaved and married respondents at the last interview. Dysphoria was defined as 2 weeks or more of feeling "sad, blue, depressed or when you lost all interest and pleasure in things you usually cared about or enjoyed"

between interview periods. Depressive episode was defined according to *DSM-III*'s guidelines for major depressive episode; in addition to meeting the dysphoria criteria, respondents also had to report symptoms in at least four of eight of the major depression symptom groups. While the DIS formally excludes depressive episodes associated with the death of a spouse, we included these episodes in order to assess the nature and extent of depression in the newly bereaved.

Several sociodemographic factors (i.e., sex, age, race, and household size) were entered into the statistical models by using logistic regression in order to 1) control for variation from the population introduced by the sampling design and 2) test possible risk factors, as suggested by others (3, 4, 10–12). Logistic regression models were also used to contrast symptoms between the newly widowed and married groups.

## RESULTS

Among the 1,180 men and women 45 and older who completed the three waves of interviews, 39 were widowed during the course of the study period. The bereaved respondents were older (mean  $\pm$  SD age =  $73.4 \pm 6.9$  years compared to  $65.2 \pm 9.4$  years;  $t=7.20$  [unequal variance],  $df=43$ ,  $p<0.001$ ), more likely to be women (61.5% [ $N=24$ ] versus 41.1% [ $N=469$ ];  $\chi^2=5.66$ ,  $df=1$ ,  $p<0.05$ ), and living with fewer people in their household at the start of the study period ( $\chi^2=20.93$ ,  $df=2$ ,  $p<0.001$ ). None of the newly bereaved were black.

Although both the bereaved and married groups were equally likely to have reported a previous episode of dysphoria at the time of their first interview (17.9% [ $N=7$ ] versus 23.0% [ $N=262$ ]; *n.s.*), none of the bereaved reported a prior depressive episode (compared to 2.9% [ $N=33$ ] of the married subjects). Since all of the newly bereaved were nonblack and had no history of depressive episodes, subsequent comparisons examined only nonblack respondents without a history of depression ( $N=1,086$ ).

By the third interview (table 1), the majority of the newly bereaved reported dysphoria, i.e., 2 weeks or



more of sadness during the study period. The newly bereaved were much more likely to report dysphoria than the married group. A smaller percentage of the newly bereaved reported an episode of depression during the study period; but the newly bereaved were more likely to report depression than the married group. Adjustments for sex, age, and household size reduced the odds ratio minimally (see table 1). Further adjustments for a history of dysphoria increased the risk of dysphoria and depression attributable to bereavement.

In both the newly bereaved and married groups, women had a greater risk of dysphoria and depressive episodes. Neither age nor household size affected the risk for either dysphoria or depressive episodes. We found no statistically significant interactions between the effects of bereavement and any of the demographic factors for either dysphoria or depressive episode.

Next, we examined whether the effects of a history of dysphoria on the risk of a recent (within the year) dysphoria or depressive episode were similar between the newly bereaved and their married counterparts. We found that a reported history of dysphoria increased the risk of recent dysphoria to the same extent for the two groups. In contrast, whether or not a respondent reported past dysphoria differentially affected the risk of a depressive episode for the two groups. Of the sample, 28.1% (N=9 of 32) of the bereaved and 0.7% (N=6 of 824) of the married subjects without a history of dysphoria reported a recent depressive episode, compared with 42.9% (N=3 of 7) of the bereaved and 12.1% (N=27 of 223) of the married subjects with a history of dysphoria. Bereavement posed a substantially higher risk of a depressive episode for those men and women who did not report past dysphoria (unadjusted odds of 55.4, 95% confidence interval=17.1–67.3;  $\chi^2=49.04$ ,  $df=1$ ,  $p<0.001$ ) than for those who did report past dysphoria (unadjusted odds of 5.5, 95% confidence interval=1.1–26.3;  $\chi^2=4.59$ ,  $df=1$ ,  $p<0.05$ ). The difference between the odds ratios was reduced somewhat when they were adjusted for sex, age, and household size (adjusted odds of 45.2 [95% confidence interval=17.6–115.6] and 11.9 [2.0–70.8], respectively); and the interaction remained significant ( $\chi^2=3.94$ ,  $df=1$ ,  $p<0.05$ ).

Although we do not have the exact date that each respondent lost his or her spouse, we were able to use the multiple waves of New Haven data to approximate the proximity of loss of spouse to the occurrence of a depressive episode. Of the 39 newly bereaved, 21 had lost their spouses during the first 6 months of the study; six of these 21 (29%) reported a depressive episode during this same period. The depressive episode lasted into the second 6-month period of the study for only two of these six (10% of the 21 bereaved during the first six months) respondents. Neither of these widows reported their depression lasting until the 2-week period before the final interview. At the final interview, the one widow (5% of the 21) reporting a current episode of depression had no prior depression.

**TABLE 2. Depressed Bereaved and Married Adults Reporting Symptoms From Each DSM-III Depressive Symptom Group During the Worst Episode**

Symptom	Married (N=33) <sup>a</sup>		Bereaved (N=12)	
	N	%	N	%
Appetite/weight	25	76	11	92
Appetite loss	17	52	8	67
Weight loss	9	27	4	33
Weight gain	6	18	1	8
Sleep disturbance	28	85	10	83
Insomnia	27	82	9	75
Sleep too much	4	12	1	8
Psychomotor disturbance	21	64	8	67
Move slowly	16	48	7	58
Move all the time	9	27	4	33
Loss of interest	15	45	3	25
Fatigue	22	67	8	67
Feelings of worthlessness/ guilt	15	47	1	8 <sup>b</sup>
Diminished concentration	25	76	6	50
Trouble concentrating	22	67	5	42
Slow thinking	18	55	6	50
Suicidal ideation	23	72	10	83
Thoughts of death	19	59	9	75
Want to die	9	28	3	25
Thought of suicide	5	16	0	0
Attempted suicide	0	0	0	0

<sup>a</sup>Because of missing data, N=32 for feelings of worthlessness/guilt and suicidal ideation.

<sup>b</sup> $\chi^2=4.06$ ,  $df=1$ ,  $p<0.05$  for bivariate relationship;  $\chi^2=3.62$ ,  $df=1$ ,  $p<0.06$  when age, sex, and household size were controlled for.

The remaining 18 bereaved had lost their spouses in the second 6 months of the study; four of these 18 (22%) reported a depressive episode during this same period. Of these four respondents, three were still depressed at the time of the final interview (17% of these 18 respondents). Only one respondent (6%) reported a depressive episode before the spouse's death (in the first 6 months of the study), and this widow did not report any subsequent depression.

We compared symptoms from each of the eight DSM-III depressive symptom groups for the widowed and married respondents who met the criteria for major depressive episode (table 2). There were no significant differences in reported neurovegetative symptoms, psychomotor disturbance, or suicidal ideation. The only statistical difference was the lack of feelings of guilt or worthlessness among the bereaved.

## DISCUSSION

These findings from the community sample of respondents in the New Haven Epidemiologic Catchment Area are consistent with other studies that report high prevalence rates of depressive symptoms among the newly bereaved. In this study almost two-thirds of the newly widowed reported a 2-week period or more of dysphoria, substantially more than their married counterparts. In addition, almost one-third of all

newly bereaved report depressive symptoms severe enough to have met *DSM-III* criteria for a major depressive episode, a figure consistent with other reports (1–3, 13, 14). In the present study the effects of bereavement on dysphoria and depression were consistent across sex, age, and household size.

Our comparison of specific depressive symptoms also confirms *DSM-III* and prior research (3) indicating that the majority of subjects depressed during bereavement differ from subjects with other major depressive episodes by lacking feelings of guilt or worthlessness. We found no apparent difference in psychomotor retardation. No one in the study sample reported ever attempting suicide. While none of the bereaved reported suicidal thoughts, the majority reported thoughts about death only.

One of the advantages of using the data from the Epidemiologic Catchment Area Program is the prebereavement evaluation of psychiatric status. None of the bereaved, and few of the married respondents, in this subsample had experienced a prior depressive episode. Because the lifetime rate of depressive episodes in our study sample was low, the absence of past episodes among the bereaved is not surprising. The rate of past depression did not differ significantly between the bereaved and married respondents (0.0% versus 3.1%;  $\chi^2=0.39$ ,  $df=1$ ,  $p=0.53$ ). As a result, however, we are not able to examine the effect of past history of depression on bereavement outcomes. The data do indicate that prior history of depressive episodes cannot adequately explain who among the bereaved were at risk for a depressive response to their loss.

We were able, however, to examine the effect of past history of dysphoria. While past history of dysphoria increased the risk of depression for both the married and bereaved, bereavement was a greater risk factor for a depressive episode for those who had not reported past dysphoria than for those who had. This counterintuitive result further affirms the situationally specific nature of the depressions of bereavement and suggests questions for future research. We may learn, for example, that past dysphoria is associated with anticipatory grief, although the effects of anticipated death on grief reactions are not yet well understood (4, 15, 16).

In closing, these data indicate that a substantial proportion of the newly widowed report symptoms that in another context would be considered a major depressive episode according to *DSM-III-R*. We still need to understand more about the short- and long-term effects that these syndromes have on the lives of the newly bereaved, compared to those with more mild and transient reactions, in order to judge their implications. Finally, practitioners should continue to mon-

itor those newly bereaved who exhibit numerous and prolonged depressive symptoms, including those without past histories of depressive symptoms, for other possible negative outcomes (17).

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#### REFERENCES

1. Osterweis M, Solomon F, Green M (eds): Bereavement: Reactions, Consequences, and Care. Washington, DC, National Academy Press, 1984
2. Clayton PJ: The sequelae and nonsequelae of conjugal bereavement. *Am J Psychiatry* 1979; 136:1530–1534
3. Clayton PJ: Bereavement, in *Handbook of Affective Disorders*. Edited by Paykel ES. New York, Guilford Press, 1982
4. Breckenridge JN, Gallagher DE, Thompson LW, et al: Characteristic depressive symptoms of bereaved elders. *J Gerontol* 1986; 41:163–168
5. Gallagher DE, Thompson LW, Peterson JA: Psychosocial factors affecting adaptation to bereavement in the elderly. *Int J Aging Hum Dev* 1981–1982; 14:79–95
6. Eaton WW, Kessler LG (eds): *Epidemiologic Methods in Psychiatry: The NIMH Epidemiologic Catchment Area Program*. New York, Academic Press, 1985
7. Leaf PJ, Myers JK: Procedures used in the epidemiologic catchment area studies, in *Psychiatric Disorders in America*. Edited by Robins L, Regier D. New York, Free Press (in press)
8. Bruce ML, Leaf PJ: Psychiatric disorders and 15-month mortality in a community sample of older adults. *Am J Public Health* 1989; 79:727–730
9. Robins LN, Helzer JE, Croughan J, et al: National Institute of Mental Health Diagnostic Interview Schedule: its history, characteristics, and validity. *Arch Gen Psychiatry* 1981; 38:381–389
10. Gallagher DE, Breckenridge JN, Thompson LW, et al: Effects of bereavement on indicators of mental health in elderly widows and widowers. *J Gerontol* 1983; 38:565–571
11. Bornstein PE, Clayton PJ, Halikas JA, et al: The depression of widowhood after thirteen months. *Br J Psychiatry* 1973; 122:561–566
12. Richards JG, McCallum J: Bereavement in the elderly. *NZ Med J* 1979; 89:201–204
13. Jacobs SC, Hansen F, Berkman L, et al: Depressions of bereavement. *Compr Psychiatry* 1989; 30:218–224
14. McHorney CA, Mor V: Predictors of bereavement depression and its health services consequences. *Med Care* 1988; 26:882–893
15. Gerber I, Rusalew R, Hannon N, et al: Anticipatory grief and aged widows and widowers. *J Gerontol* 1975; 30:225–229
16. Norris FH, Murrell SA: Older adult family stress and adaptation before and after bereavement. *J Gerontol* 1987; 42:606–612
17. Jacobs SC, Ostfeld A: The clinical management of grief. *J Am Geriatr Soc* 1980; 28:331–335

# Mortality in a Group of Formerly Incarcerated Juvenile Delinquents

Catherine A. Yeager, M.A., and Dorothy Otnow Lewis, M.D.

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*A 7-year follow-up study of formerly incarcerated delinquents revealed an extremely high mortality rate. Of 118 male and female subjects, seven had died before their 25th birthdays, making the mortality rate of the sample approximately 58 times the national average for individuals in their age group. All died violent deaths, making the violent death rate of the sample approximately 76 times the national average for that age group. Differences in mortality rates according to the race and sex of the subjects are reported, and possible clinical predictors of early death are explored.*

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In previous articles (1-3), Lewis and Shanok reported the extremely adverse medical histories of samples of juvenile delinquents compared to those of demographically comparable nondelinquents. From infancy onward, delinquents suffered more serious accidents, injuries, and illnesses than did their nondelinquent counterparts. The purpose of this article is to report an unusually high mortality rate in a group of 118 formerly incarcerated delinquents whose clinical histories have been previously described (4-6) and to explore possible factors that place such delinquents at risk for early violent death.

At a time when the violent death rate for the total U.S. population is decreasing, there is a disturbing increase in the rate of violent death (i.e., homicide, suicide, and accidents) among the young (7). Whereas heart disease and cancer are the leading causes of death in the U.S. population as a whole, within the 15- to 24-year-old age group, accidents are the most common cause of death (51.0/100,000), followed by homicide (13.9/100,000) and suicide (13.0/100,000) (8).

Between the 1950s and the mid-1980s, there was a doubling of the homicide rate and a tripling of the suicide

rate among young people (7, 9, 10). When rates are calculated according to race and sex, the leading cause of death for black males under the age of 25 is homicide (79.6/100,000; for white males the homicide rate is 12.3/100,000). For white males of the same age group, the leading cause of death is accidents (82.3/100,000; the accident rate for black males is 57.1/100,000). The suicide rate for young black males is approximately half the rate for young white males (11.5/100,000 versus 23.3/100,000). In the aggregate, nonwhite males have the highest violent death rates, followed by white males, white females, and nonwhite females (8).

Mortality statistics for adolescents and young adults reflect general trends. The question remains whether there are subgroups within the adolescent population who are at especially high risk for early violent death and who contribute inordinately to the rising mortality rates in this age group. This article focuses on one subgroup of young people, former seriously delinquent juveniles.

## METHOD

Our sample consisted of 118 juveniles (97 males and 21 females) who were incarcerated during the late 1970s in the only correctional school in Connecticut. Their mean  $\pm$  SD age at the time of incarceration was  $15.25 \pm 1$  years. When incarcerated, they received comprehensive psychiatric, neurological, and psychoeducational evaluations as part of a study documenting the neuropsychiatric, psychoeducational, and family characteristics of incarcerated delinquents (4).

Approximately 7 years after the original study, attempts were made to locate all of the subjects for a follow-up study. In the course of trying to locate these subjects, we checked death certificates from the state in which the subjects resided when they were incarcerated as juveniles. Information regarding the subjects' deaths was also gathered from friends and relatives and occasionally from newspaper reports. Because we were unable to obtain access to a national database of death certificate information, we could not be certain of the status of seven subjects who had moved out of the state. As a result, our findings may be an underestimate of the actual death rate for this group of former delinquents.

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Received May 3, 1989; revision received Oct. 2, 1989; accepted Nov. 8, 1989. From the Department of Psychiatry, New York University School of Medicine. Address reprint requests to Ms. Yeager, Department of Psychiatry, New York University Medical Center, New Bellevue, 21525, 550 First Ave., New York, NY 10016.

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TABLE 1. Demographic Characteristics, Causes of Death, and Violence Ratings of Seven Formerly Incarcerated Juvenile Delinquents

Subject	Race	Sex	Cause of Death	Age at Death	Violence Rating in Adolescence (scale of 0–4)
1	Black	Male	Stabbed in jail by inmate	23	4
2	Black	Male	Collision between bicycle and automobile	16	4
3	Hispanic	Male	Shot by police	15	3
4	Hispanic	Male	Acetaminophen overdose	21	3
5	White	Male	Suicide by hanging	24	1
6	White	Male	Motorcycle accident	21	3
7	White	Female	Cocaine overdose	21	3

## RESULTS

Of the 118 subjects, we found that six males and one female had died before their 25th birthdays, making the mortality rate of our sample of formerly incarcerated delinquents seven of 118, or 5,932/100,000. This was 58 times the national mortality rate for 15- to 24-year-olds (i.e., 101.6/100,000) (8).

As can be seen in table 1, all who died met violent ends, making the violent death rate of our sample synonymous with its overall mortality rate. Thus, the violent death rate in our group (5,932/100,000) was 76 times the violent death rate of individuals 15–24 years of age in the general population (i.e., 77.9/100,000) (8).

When the mortality rate of our sample was broken down in terms of sex and race, we found that the rate for nonwhite male subjects was 37 times the national average for nonwhite males of that age group (i.e., 6,557/100,000 versus 178/100,000 [8]). The mortality rate for white male subjects was 38 times the national average for young white males (i.e., 5,556/100,000 versus 145/100,000 [8]). Thus, both white and minority males were at extraordinary risk for violent death in comparison with their nondelinquent peers.

Only one of the 21 females, a white subject, was dead at the time of follow-up, making the female mortality rate of our sample 4,762/100,000; the rate for females in the general population is 52/100,000 (8). Although it would be imprudent to infer, solely on the basis of the one girl who died, that female delinquents are at great risk for early death, it should be mentioned that another young woman, also a white subject, had contracted acquired immune deficiency syndrome (AIDS) from prostitution and/or chronic intravenous drug use and was near death at the time of this study. Had this subject been included in our calculations, the mortality rate of the delinquent females would have been 9,524/100,000, making the female delinquent mortality rate the highest for all subjects.

In our previous studies (11, 12), certain constellations of biopsychosocial variables distinguished youngsters who went on to commit violent offenses from those who did not. We wondered whether the same kinds of vulnerabilities that distinguished violent from less violent subjects (i.e., psychotic symptoms, neurological impairment, cognitive dysfunction, and an abu-

sive, violent upbringing) would distinguish the subjects who died young, and by violent means, from those who survived. Such was not the case. None of these variables, alone or in combination, significantly distinguished the dead subjects from the rest of the group.

Did previous suicide attempts distinguish the seven subjects who died from the other subjects? Of the seven dead subjects, none of the males had attempted suicide in adolescence. The female subject who died had attempted suicide; however, so had the majority (N=17, 81%) of the female delinquents. Thus, in this delinquent sample, previous suicide attempts, in most cases, were not harbingers of early death.

Did degree of violence distinguish the youngsters who were at highest risk? In our previous study (4), the subjects' aggressive behaviors had been rated on a violence scale from 1 to 4 in order of increasing severity. As can be seen in table 1, all but one of the dead subjects received ratings of 3 or 4 and so were among the more violent delinquents; however, the majority of the delinquents had received violence ratings of 3 or 4. Thus, degree of violence was not an accurate predictor of early death, at least among these already incarcerated delinquents.

We wondered whether parental mental illness, as reflected in previous parental psychiatric hospitalizations, had placed the dead subjects at higher risk for early death than the rest of the group of delinquents. Of the seven dead subjects, two (29%) had a parent who had a psychiatric hospitalization; of the remaining 111 subjects, 28 (25%) had at least one parent who had had a psychiatric hospitalization. Thus, documented serious psychopathology in a parent did not differentiate the groups.

It should be noted that two (29%) of the seven dead subjects had experienced the death of a parent before they were incarcerated; in contrast, 10 (9%) of the remaining 111 subjects had had this experience ( $p=0.126$ , Fisher's exact test). The two youngsters who had lost a parent were among the three subjects who committed suicide.

## DISCUSSION

Were there any early indicators that might have revealed which delinquent youngsters were at greatest



risk for premature death? In only one case had there been a clear predictor—an actual suicide attempt that should have alerted caretakers. Two of the three subjects who committed suicide had had a parent who died, a finding consistent with the literature on adolescent suicide (13–15) and one that might have served as a warning. Both of the youngsters who were murdered were extremely paranoid and had been shot at in the past. Should these characteristics have singled them out as especially vulnerable? The two accident victims had substantial neurological impairment; both were microcephalic, had a multiplicity of soft neurological signs, and were described as extremely impulsive. Might this clinical picture have been used as a predictor of accidental death? In short, would an earlier recognition of these potentially important indicators have enabled caretakers to identify and given special attention to those delinquents who were at highest risk for early violent death?

Further examination of the records of the entire sample showed that similar proportions of living subjects had comparable histories of suicide attempts, early parental loss, paranoid symptoms, and neurological impairment. Most were considered impulsive and violent; in fact, many youngsters had been shot at, stabbed, and otherwise attacked before their incarceration as juveniles. We were unable to extract from our rich clinical database any factors that clearly distinguished the dead youngsters from the delinquents who survived into adulthood. These findings are consistent with those of Marohn et al. (16); they too were unable to find readily identifiable predictors of early death among psychiatrically hospitalized antisocial adolescents.

If our sample of Connecticut juveniles is representative of the incarcerated delinquent population in the United States—and from our own work with delinquent youth in other states (17–19) and the work of others (16, 20), we have reason to believe it is—then we have to conclude that all seriously delinquent adolescents, black and white, male and female, are at extremely high risk for early violent death. The finding that within our sample, violent behaviors were not statistically associated with early violent death flies in the face of common sense. Because the majority of these incarcerated delinquents were so aggressive, and only seven had died by the time of follow-up, it is likely that differences in degree of violence were not yet reflected in the mortality rates. We suspect that as this sample is followed over time, the effects of especially violent life styles on mortality will become evident.

At this time, however, we are unable to find any clear predictors of early death in our incarcerated delinquent sample. Therefore, we believe that all seriously delinquent youths should be considered to be at special risk. Furthermore, it is very likely that the inordinately high violent death rate for adolescents and young adults in the United States is influenced dispropor-

tionately by the high mortality rate of seriously delinquent juveniles.

## REFERENCES

1. Lewis DO, Shanok SS: Medical histories of delinquent and non-delinquent children: an epidemiological study. *Am J Psychiatry* 1977; 134:1020–1025
2. Shanok S, Lewis DO: Medical histories of abused delinquents. *Child Psychiatry Hum Dev* 1981; 11:222–231
3. Lewis DO, Shanok SS, Balla DA: Perinatal difficulties, head and face trauma, and child abuse in the medical histories of seriously delinquent children. *Am J Psychiatry* 1979; 136:419–423
4. Lewis DO, Shanok S, Pincus JH, et al: Violent juvenile delinquents: psychiatric, neurological, psychological, and abuse factors. *J Am Acad Child Psychiatry* 1979; 18:307–319
5. Lewis DO, Shanok S, Pincus JH: A comparison of the neuropsychiatric status of female and male incarcerated delinquents: some evidence of sex and race bias. *J Am Acad Child Psychiatry* 1982; 21:190–196
6. Lewis DO, Shanok S, Pincus JH, et al: The medical assessment of seriously delinquent boys: a comparison of pediatric, psychiatric, neurologic, and hospital record data. *J Adolesc Health Care* 1982; 3:160–164
7. Holinger PC: Self-destructiveness among the young: an epidemiological study of violent deaths. *Int J Soc Psychiatry* 1981; 27:277–282
8. National Center for Health Statistics: *Vital Statistics of the United States, vol II:—Mortality, 1986*. Hyattsville, Md, Public Health Service, 1986
9. Weiss NS: Recent trends in violent deaths among young adults in the United States. *Am J Epidemiol* 1976; 103:416–422
10. Holinger PC: *Violent Deaths in the United States*. New York, Guilford Press, 1987, p 16
11. Lewis DO, Moy E, Jackson LD, et al: Biopsychosocial characteristics of children who later murder: a prospective study. *Am J Psychiatry* 1985; 142:1161–1167
12. Lewis DO, Lovely R, Yeager C, et al: Toward a theory of the genesis of violence: a follow-up study of delinquents. *J Am Acad Child Adolesc Psychiatry* 1989; 28:431–436
13. Pfeffer CR: Parental suicide: an organizing event in the development of latency age children. *Suicide Life Threat Behav* 1980; 11:43–50
14. Cohen-Sandler R, Berman A, King RA: Life stress and symptomatology: determinants of suicidal behavior in children. *J Am Acad Child Adolesc Psychiatry* 1982; 21:178–186
15. Pfeffer CR, Zuckerman S, Plutchik R, et al: Suicidal behavior in normal school children: a comparison with child psychiatric inpatients. *J Am Acad Child Adolesc Psychiatry* 1984; 23:416–423
16. Marohn RC, Loche EM, Rosenthal R, et al: Juvenile delinquents and violent death. *Adolesc Psychiatry* 1982; 10:147–170
17. Bernhard M: *Activating variables and inhibitory deficits associated with violent male juvenile delinquents (doctoral dissertation)*. New York, New York University, Department of Psychology, 1987
18. Lewis DO, Pincus JH, Bard B, et al: Neuropsychiatric, psychoeducational, and family characteristics of 14 juveniles condemned to death in the United States. *Am J Psychiatry* 1988; 145:584–589
19. Lewis DO, Lovely R, Yeager C, et al: Intrinsic and environmental characteristics of juvenile murderers. *J Am Acad Child Adolesc Psychiatry* 1988; 27:582–587
20. Robins LM: *Deviant Children Grown Up: A Sociological and Psychiatric Study of Sociopathic Personality*. Baltimore, Williams & Wilkins, 1966

# Addition of Lithium Carbonate to Carbamazepine: Hematological and Thyroid Effects

Keith G. Kramlinger, M.D., and Robert M. Post, M.D.

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*In view of the increasing use of lithium-carbamazepine combination therapy for refractory psychiatric disorders, the authors assessed the clinical laboratory effects of adding lithium to carbamazepine in 23 patients with affective disorders. Lithium produced a robust reversal of carbamazepine-induced leukopenia, increasing WBCs, predominantly neutrophils, to levels significantly above placebo baseline values. The combination produced additive antithyroidal effects, resulting in greater decreases in  $T_4$  and free  $T_4$  than with carbamazepine alone; the addition of lithium was associated with the emergence of a modestly higher TSH level. The authors discuss clinical and theoretical implications of these findings.*

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Lithium carbonate is the treatment of choice for bipolar affective disorder. Carbamazepine, an anti-convulsant, is currently the most intensively studied treatment alternative to lithium, particularly for lithium-resistant bipolar disorder (1-4). The two drugs show a similar spectrum of clinical efficacy in the treatment of acute mania and prophylaxis against recurrent affective episodes; to a lesser extent, each drug used alone may be effective in the treatment of acute depression.

Clinical efficacy of the combined use of carbamazepine and lithium, in instances when each drug used alone was ineffective, has been reported in the treatment of acute mania and acute depression and in the prophylaxis against recurrent affective episodes (for reviews see references 5 and 6). Despite infrequent reports of neurotoxicity associated with the carbamazepine-lithium combination, the majority of reports in the literature suggest that this combination is safe and well tolerated (7).

When used alone, lithium and carbamazepine exert effects on physiologic systems that may be reflected in several clinical laboratory measures, including hematological and thyroid indices. For example, lithium

commonly induces a relative leukocytosis (8), whereas carbamazepine consistently decreases leukocytes (9, 10). Also, lithium is associated with a notable (7%-8%) incidence of hypothyroidism (11, 12), whereas carbamazepine is not (13); although these drugs reduce peripheral thyroid hormone levels to similar degrees, lithium treatment is associated with increases of thyroid-stimulating hormone (TSH) levels (14) but carbamazepine is not (13).

In view of these known and sometimes opposite clinical laboratory effects of lithium and carbamazepine when used alone and the increasing use of these two agents in combination in treatment-resistant patients, we investigated the effects of adding lithium carbonate to carbamazepine on hematological measures and thyroid indices.

## METHOD

The patients met the *DSM-III* criteria for major affective disorder and gave oral and written informed consent for a clinical trial of carbamazepine and associated research procedures. A thorough neurological history and examination and a pretreatment EEG helped rule out the presence of a seizure disorder or related medical condition.

After a placebo period, treatment with carbamazepine was initiated on a double-blind basis at a dose of 200-400 mg/day and slowly increased until clinical response occurred, side effects supervened, or a dose limit of 1600 mg/day was achieved. Plasma levels were generally between 4 and 12  $\mu\text{g/ml}$ , but after initial findings indicated a poor relationship between blood levels and clinical response (15), blood levels were not used as a major determinant of dose adjustment. After chronic treatment for an acute episode, 15 depressed patients and seven manic patients with inadequate clinical responses to carbamazepine or no response were given lithium carbonate, also on a blind basis, at doses of 300-600 mg/day, and each patient's dose was slowly increased until clinical response occurred, side effects supervened, or a maximum plasma lithium level of 1.2 meq/liter was attained. As discussed in detail elsewhere (5, 6), eight of the 15 depressed patients and six of the seven manic patients who had had inadequate responses to carbamazepine alone improved af-

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Received Feb. 15, 1989; revision received Oct. 25, 1989; accepted Nov. 21, 1989. From the Biological Psychiatry Branch, NIMH. Address reprint requests to Dr. Post, Biological Psychiatry Branch, NIMH, Bldg. 10, Rm. 3N212, 9000 Rockville Pike, Bethesda, MD 20892.

ter the addition of lithium. We also included one euthymic patient who experienced occasional 1–2-day periods of hypomania while receiving carbamazepine only, bringing to 23 the total number of patients studied. There were 17 women and six men in the study, and their mean $\pm$ SD age was 40.0 $\pm$ 12.7 years (range, 20–60). Twenty-one patients had bipolar disorders (17 bipolar I and four bipolar II) and two had unipolar disorders.

The duration of carbamazepine treatment before lithium supplementation ranged from 11 to 343 days; the median was 39 days, and the mean $\pm$ SD was 67 $\pm$ 83 days. During the last week of carbamazepine monotherapy, the mean $\pm$ SD carbamazepine dose was 1022 $\pm$ 370 mg/day (range, 300–1600); the blood level was 8.8 $\pm$ 2.5  $\mu$ g/ml (range, 3.1–12.4) at this time and did not change significantly during lithium supplementation. During the first week of combination treatment, the lithium dose was 809 $\pm$ 310 mg/day (range, 171–1543) and the plasma lithium level was 0.61 $\pm$ 0.22 meq/liter (range, 0.1–1.1). Between the first and second weeks of combination treatment there were significant increases in both lithium dose (976 $\pm$ 323 mg/day) ( $t=5.01$ ,  $df=22$ ,  $p<0.0001$ ) and blood level (0.78 $\pm$ 0.29 meq/liter) ( $t=4.54$ ,  $df=19$ ,  $p<0.0002$ ), and these increases persisted for the duration of the study.

Four patients were treated with additional medications during portions of the carbamazepine treatment period; three patients received thyroid supplementation and one patient received thioridazine for psychosis. The concurrent thyroid medications did not produce adequate responses and were discontinued in two of the three cases before lithium supplementation; the remaining patient continued to receive thyroxine for the duration of the study period. These three patients were excluded from the analysis of medication effect on thyroid function. One postmenopausal patient received replacement estrogen treatment for the duration of her hospitalization.

Blood samples were obtained at approximately weekly intervals during the placebo period, carbamazepine monotherapy, and carbamazepine-lithium combination therapy for CBCs, WBC differential counts, and measurement of  $T_4$ , free  $T_4$ ,  $T_3$ , and TSH. Values were determined by means of radioimmunoassay for  $T_4$ ,  $T_3$ , and TSH, by equilibrium dialysis for free  $T_4$ , and by atomic absorption spectrophotometry for lithium. Plasma carbamazepine levels were determined by means of radioenzymatic assay or high-performance liquid chromatography.

The data were analyzed with paired  $t$  tests in the comparisons of values in the placebo, carbamazepine, and carbamazepine-lithium periods. To conservatively assess medication effects and facilitate the presentation of data on these multiple clinical laboratory measures, means of values from the final 3 weeks of carbamazepine monotherapy and from the first 3 weeks of carbamazepine-lithium therapy were also used in statistical analyses. When comparing the values of the various

subgroups (e.g., responders and nonresponders, depressed and manic), group  $t$  tests were employed. Correlations between changes in hematological indices and lithium dose and blood level were determined by means of Pearson's correlations.

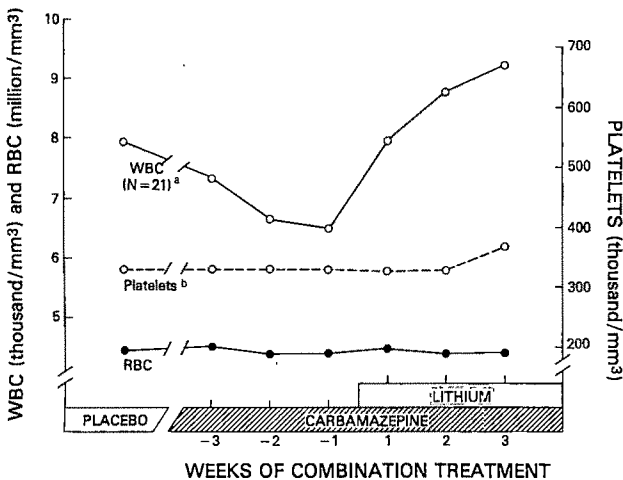
## RESULTS

The mean total WBC count during the final 3 weeks of carbamazepine monotherapy was significantly lower than the value during the placebo baseline period ( $t=2.51$ ,  $df=19$ ,  $p<0.03$ ). The lymphocyte count was also significantly lower ( $t=3.50$ ,  $df=16$ ,  $p<0.003$ ), and a trend toward fewer neutrophils was observed ( $t=2.04$ ,  $df=16$ ,  $p<0.06$ ). The numbers of eosinophils, basophils, and monocytes were not significantly altered by carbamazepine. Comparison of the WBC differential counts revealed no significant differences.

Lithium not only reversed the WBC suppression caused by carbamazepine, but also increased the values above those before treatment. Compared with the mean value for the last 3 weeks of carbamazepine monotherapy, the mean total WBC count for the first 3 weeks of carbamazepine-lithium combination therapy was significantly higher ( $t=-5.83$ ,  $df=21$ ,  $p<0.0002$ ). Increases in numbers of neutrophils ( $t=-4.65$ ,  $df=19$ ,  $p<0.0002$ ) and eosinophils ( $t=-2.83$ ,  $df=19$ ,  $p<0.02$ ) were observed after the addition of lithium; the numbers of basophils, monocytes, and lymphocytes were not significantly affected. WBC differential counts during lithium potentiation revealed an increase in the percentage of neutrophils ( $t=-3.60$ ,  $df=19$ ,  $p<0.002$ ) and reductions in the percentages of lymphocytes ( $t=3.42$ ,  $df=19$ ,  $p<0.003$ ) and monocytes ( $t=2.38$ ,  $df=19$ ,  $p<0.03$ ), reflecting the robust and predominant increase in neutrophil numbers. Neither lithium dose nor plasma level was significantly correlated with degree of change in total WBC or neutrophil count.

As illustrated in figure 1, there was a progressive increase in total WBC count during lithium treatment, such that by the third week of combination treatment, the total WBC count ( $9.2\pm2.8\times1000$  cells/mm<sup>3</sup>) was significantly higher than at placebo baseline ( $7.9\pm2.5$ ) ( $t=2.92$ ,  $df=18$ ,  $p<0.01$ ). This increase in WBC count was attributable to an increase in neutrophils (figure 2) ( $t=2.47$ ,  $df=16$ ,  $p<0.05$ ).

The mean platelet counts for the last 3 weeks of carbamazepine monotherapy and the first 3 weeks of carbamazepine-lithium combination treatment were not significantly different from the value at placebo baseline. However, the platelet count during the third week of lithium potentiation ( $367\pm88$ /mm<sup>3</sup>) was significantly higher than the mean for the final 3 weeks of carbamazepine monotherapy ( $325\pm95$ /mm<sup>3</sup>) ( $t=2.68$ ,  $df=20$ ,  $p<0.05$ ) (see figure 1). This increase was not correlated with either lithium dose or plasma level. The RBC counts were not significantly changed from the placebo baseline value during the carbamazepine

**FIGURE 1. Mean Values for Hematological Indices During Lithium Potentiation of Carbamazepine in 23 Patients With Affective Disorders**

<sup>a</sup>Significant differences: placebo versus week -1 ( $t=4.67$ ,  $df=16$ ,  $p<0.001$ ); mean of values for last 3 weeks of carbamazepine versus week 1 ( $t=3.59$ ,  $df=20$ ,  $p<0.01$ ), week 2 ( $t=5.54$ ,  $df=20$ ,  $p<0.001$ ), and week 3 ( $t=4.97$ ,  $df=20$ ,  $p<0.001$ ).

<sup>b</sup>Significant difference: mean for last 3 weeks of carbamazepine treatment versus week 3 ( $t=2.68$ ,  $df=20$ ,  $p<0.05$ ).

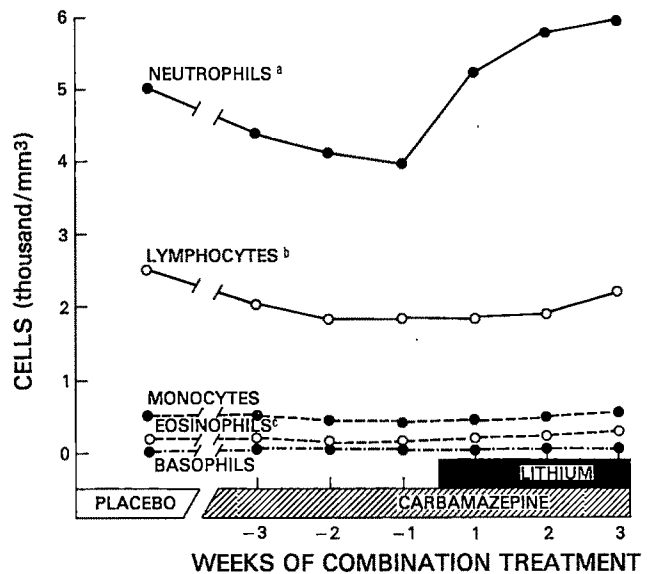
monotherapy and carbamazepine-lithium combination treatment periods.

Between baseline and the final 3 weeks of carbamazepine monotherapy, there were significant reductions in  $T_4$  ( $t=6.23$ ,  $df=10$ ,  $p<0.0001$ ), free  $T_4$  ( $t=4.88$ ,  $df=11$ ,  $p<0.0005$ ), and  $T_3$  ( $t=3.07$ ,  $df=10$ ,  $p<0.01$ ). No significant change in TSH was detected. During the first 3 weeks after lithium was added, there were further decreases in  $T_4$  ( $t=4.20$ ,  $df=15$ ,  $p<0.0009$ ), free  $T_4$  ( $t=2.84$ ,  $df=15$ ,  $p<0.02$ ), and  $T_3$  ( $t=1.84$ ,  $df=15$ ,  $p<0.09$ ). The mean TSH level during the first 3 weeks of carbamazepine-lithium combination therapy was significantly higher than the mean for the last 3 weeks of carbamazepine monotherapy ( $t=-3.16$ ,  $df=15$ ,  $p<0.007$ ) (figure 3). Thyroid-binding globulin values did not differ between the placebo baseline, carbamazepine monotherapy, and carbamazepine-lithium combination treatment periods.

## DISCUSSION

These data indicate that the addition of lithium carbonate to a stable carbamazepine regimen is associated with several significant clinical laboratory effects involving hematological and thyroid indices.

Carbamazepine monotherapy was associated with significant reductions in total WBC, neutrophil, and lymphocyte counts, which is consistent with previous reports (9, 10, 16). The addition of lithium carbonate to carbamazepine was associated with robust increases in total WBC count, total neutrophil count, and percentage of neutrophils over those in the final weeks of

**FIGURE 2. Mean Values for Differential WBC Counts During Lithium Potentiation of Carbamazepine in 23 Patients With Affective Disorders**

<sup>a</sup>Significant differences: placebo versus week -3 ( $t=-2.63$ ,  $df=12$ ,  $p<0.05$ ) and week -1 ( $t=-2.24$ ,  $df=14$ ,  $p<0.05$ ); mean of values for last 3 weeks of carbamazepine versus week 1 ( $t=3.08$ ,  $df=17$ ,  $p<0.01$ ), week 2 ( $t=4.32$ ,  $df=18$ ,  $p<0.001$ ), and week 3 ( $t=3.87$ ,  $df=18$ ,  $p<0.01$ ).

<sup>b</sup>Significant differences: placebo versus week -2 ( $t=-2.31$ ,  $df=14$ ,  $p<0.05$ ) and week -1 ( $t=-3.40$ ,  $df=14$ ,  $p<0.01$ ).

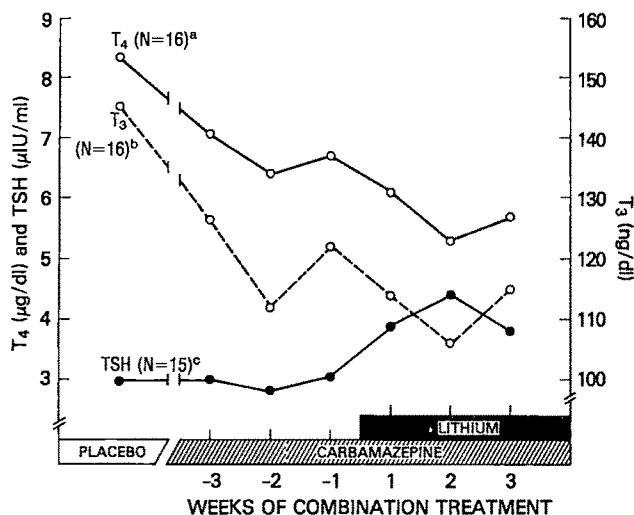
<sup>c</sup>Significant differences: mean for last 3 weeks of carbamazepine versus week 2 ( $t=2.91$ ,  $df=18$ ,  $p<0.01$ ) and week 3 ( $t=2.81$ ,  $df=18$ ,  $p<0.05$ ).

carbamazepine monotherapy. These results are consistent with previous reports of a relative leukocytosis characterized by neutrophilia during treatment with lithium alone (8). Our results are similar to those of others (16–18) who have observed a lithium-induced neutrophilic leukocytosis during carbamazepine-lithium combination treatment.

Furthermore, we found that the total WBC and neutrophil counts during carbamazepine-lithium combination treatment were higher than during the baseline placebo period, as did Joffe (16). Mastrosimone et al. (17) found that lithium supplementation returned the WBC counts to precarbamazepine levels. Brewerton (18) found that one patient's WBC counts during combined carbamazepine-lithium combination therapy were intermediate between those during treatment with carbamazepine alone and lithium alone; values during a medication-free period were not reported. Our observations imply that carbamazepine does not interfere with, or at most only partially suppresses, the mechanism by which lithium induces an increase in neutrophils.

Carbamazepine-induced decreases in WBC count occur through inhibition of granulocyte-macrophage stem cells (19). Lithium is thought to increase the WBC count (i.e., the neutrophil count) largely by increasing



**FIGURE 3. Mean Values for Thyroid Indices During Lithium Potentiation of Carbamazepine in 20 Patients With Affective Disorders**

<sup>a</sup>Significant differences: placebo versus week -3 ( $t=5.93$ ,  $df=7$ ,  $p<0.001$ ), week -2 ( $t=9.01$ ,  $df=7$ ,  $p<0.0001$ ), and week -1 ( $t=4.15$ ,  $df=8$ ,  $p<0.01$ ); mean of values for last 3 weeks of carbamazepine versus week 1 ( $t=3.53$ ,  $df=14$ ,  $p<0.01$ ), week 2 ( $t=4.99$ ,  $df=12$ ,  $p<0.001$ ), and week 3 ( $t=4.86$ ,  $df=12$ ,  $p<0.001$ ).

<sup>b</sup>Significant differences: placebo versus week -2 ( $t=3.19$ ,  $df=6$ ,  $p<0.05$ ) and week -1 ( $t=2.53$ ,  $df=9$ ,  $p<0.05$ ); mean of values for last 3 weeks of carbamazepine versus week 2 ( $t=2.89$ ,  $df=12$ ,  $p<0.05$ ).

<sup>c</sup>Significant differences: mean of values for last 3 weeks of carbamazepine versus week 1 ( $t=-2.45$ ,  $df=14$ ,  $p<0.05$ ), week 2 ( $t=-2.79$ ,  $df=12$ ,  $p<0.05$ ), and week 3 ( $t=-3.57$ ,  $df=11$ ,  $p<0.01$ ).

granulocyte production rather than by redistributing granulocytes (20–22), probably directly through pluripotent stem cell stimulation (23–27) and/or enhanced production of colony-stimulating factor (28, 29).

The platelet count in our study did not vary significantly between the carbamazepine and placebo periods, a finding similar to those in previous reports (10). The addition of lithium carbonate to stable carbamazepine treatment was associated with a significant increase in platelet count by the third week of combination treatment. This effect has been reported for lithium when used alone (30) and confirms a recent report (16) of similar results in carbamazepine-treated patients undergoing lithium carbonate augmentation therapy. The mechanism for this effect may be increased bone marrow platelet production (31) through either direct stimulation of megakaryocytic stem cells and/or enhancement of the effects of megakaryocyte-colony-stimulating factor (25). Although clinically carbamazepine does not appear to have significant consistent effects on number of circulating platelets, in culture carbamazepine inhibits megakaryocyte progenitor (CFU-Meg) stem cells, an effect reversed by lithium at doses known to stimulate bone marrow function (19).

From the clinical perspective, these data suggest the utility of adding lithium to carbamazepine in cases of

isolated low WBC count. However, this would appear worth considering only when the values for other hematological indices (such as RBC count) are within normal limits and there is no evidence of a more generalized idiosyncratic response, such as aplastic anemia or systemic toxicity. Lithium does not stimulate the red cell series, and carbamazepine should be discontinued immediately if systemic toxicity is apparent.

In our study carbamazepine monotherapy was associated with significant reductions from baseline in  $T_4$ , free  $T_4$ , and  $T_3$  but no significant alterations in either TSH or thyroid-binding globulin; these findings are consistent with previous reports (13). The addition of lithium carbonate to carbamazepine was associated with a further significant decrease in  $T_4$  and free  $T_4$  (with a similar trend for  $T_3$ ), while the TSH level increased significantly. These results are consistent with previous reports of lithium's effects on thyroid function when lithium is used alone (32). Thus, the effects on thyroid function of lithium carbonate and carbamazepine appear to be additive and to occur by means of different mechanisms.

Carbamazepine's effects on peripheral thyroid hormone levels can be at least partially explained by enhanced peripheral metabolism of thyroid hormones (33, 34), although central effects cannot be ruled out (35). Direct effects of carbamazepine on thyroid gland and on carrier proteins have been excluded (33). Stimulation of liver microsomal enzymes may explain this effect (36) and has been proposed as a mechanism for the enhanced clearance and conversion of  $T_4$  to  $T_3$  during short-term phenytoin administration (37). Carbamazepine stimulates liver microsomal enzymes (38), and specific  $T_4$  deiodinating enzymes have been demonstrated in vitro in the rat liver microsomal fraction (39, 40).

Lithium affects thyroid physiology at several different levels. Lithium inhibits release of thyroid hormones from the thyroid gland (32, 41, 42), and this is probably the major thyroidal effect of lithium. Other possible mechanisms include decreases in TSH-induced cyclic adenosine monophosphate (43, 44) and inhibition of the coupling of mono- and diiodotyrosines (45).

Thus, the additive effect on thyroid function of carbamazepine-lithium combination treatment, resulting in a further decline of peripheral thyroid hormones and an increase of TSH, is not surprising, since each drug appears to act at different points in thyroid hormone physiology and metabolism and in similar directions. However, we have observed that TSH increases during combination treatment are intermediate between those during treatment with carbamazepine alone and lithium alone (Post et al., unpublished observations), despite more robust decreases in peripheral thyroid hormone concentrations with combination treatment, thus suggesting that the regulation of TSH release does not solely depend on peripheral thyroid hormone concentrations.

While the antithyroid effects of carbamazepine can

be largely ignored clinically in view of the infrequent occurrence of carbamazepine-associated hypothyroidism and the evidence that larger decreases in  $T_4$  and free  $T_4$  are associated with better acute antidepressant response (13), the effects of lithium have to be considered during combination treatment. Thyroid hormone replacement may be necessary with the use of lithium because of its associated elevations in TSH. However, even though the decreases in hormone levels appear additive, the elevations in TSH appear consistent with the effects of lithium alone, and this should be considered in relationship to possible thyroid hormone replacement during combination treatment.

In no instance in this study did carbamazepine prevent lithium's known effects on WBC count, platelet count, or thyroid function from becoming manifest. Furthermore, the fact that the total WBC and neutrophil counts in the third week of combination treatment were significantly higher than during the placebo period suggests, but does not prove, that carbamazepine does not interfere with the mechanism by which these effects of lithium occur. Thus, these clinical laboratory effects of adding lithium carbonate to carbamazepine appear to be additive, and the effects of lithium appear to supersede the effects of carbamazepine on WBC count and TSH level. This is also clearly the case for lithium-induced diabetes insipidus, where the effects of carbamazepine at or near the vasopressin receptor are insufficient to overcome the effects of lithium, which occur beyond the receptor, at the level of adenylate cyclase. The basic mechanisms underlying each clinical laboratory effect have been partially elucidated but require further study to identify precise pathophysiology.

From the clinical standpoint, the data support the possible clinical utility of adding lithium to carbamazepine for patients with WBC counts at or below the normal limit as long as other hematological values are within normal limits and not indicative of an idiosyncratic reaction. Whether lithium would also be effective in reversing the rare, idiosyncratic cases of carbamazepine-induced agranulocytosis—as suggested by others (46)—is unknown, but caution must be used before relying on this possibility (47).

Lithium potentiation of carbamazepine may be clinically effective (6, 7) and warranted in some patients. This carbamazepine-lithium combination appears to be generally well tolerated clinically in spite of occasional reports of neurotoxicity. Knowledge of the laboratory changes induced by this combination therapy is essential to adequate patient management.

#### REFERENCES

- Post RM, Ballenger JC, Uhde TW, et al: Efficacy of carbamazepine in manic-depressive illness: implications for underlying mechanisms, in *Neurobiology of Mood Disorders*. Edited by Post RM, Ballenger JC. Baltimore, Williams & Wilkins, 1984
- Post RM, Uhde TW, Roy-Byrne PP, et al: Antidepressant effects of carbamazepine. *Am J Psychiatry* 1986; 143:29–34
- Post RM, Uhde TW, Roy-Byrne PP, et al: Correlates of anti-manic response to carbamazepine. *Psychiatry Res* 1987; 21:71–83
- Post RM, Uhde TW: Clinical approaches to treatment-resistant bipolar illness, in *Psychiatry Update: American Psychiatric Association Annual Review*, vol 6. Edited by Hales RE, Frances AJ. Washington, DC, American Psychiatric Press, 1987
- Kramlinger KG, Post RM: Adding lithium carbonate to carbamazepine: antimanic efficacy in treatment-resistant mania. *Acta Psychiatr Scand* 1989; 79:378–385
- Kramlinger KG, Post RM: The addition of lithium to carbamazepine: antidepressant efficacy in treatment-resistant depression. *Arch Gen Psychiatry* 1989; 46:794–800
- Brewerton TD, Kramlinger KG, Post RM: Combination therapy with lithium and carbamazepine, in *Lithium: Inorganic Pharmacology and Psychiatric Use*. Edited by Birch NJ. Oxford, IRL Press, 1988
- Shopsin B, Friedmann R, Gershon S: Lithium and leukocytosis. *Clin Pharmacol Ther* 1971; 12:923–928
- Hart RG, Easton JD: Carbamazepine and hematological monitoring. *Ann Neurol* 1982; 11:309–312
- Joffe RT, Post RM, Roy-Byrne PP, et al: Hematological effects of carbamazepine in patients with affective illness. *Am J Psychiatry* 1985; 142:1196–1199
- Amidsen A, Andersen CJ: Lithium treatment and thyroid function: a survey of 237 patients in long-term lithium treatment. *Pharmacopsychiatry* 1982; 15:149–155
- Myers DH, Carter RA, Burns BH, et al: A prospective study of the effects of lithium on thyroid function and on the prevalence of antithyroid antibodies. *Psychol Med* 1985; 15:55–61
- Roy-Byrne PP, Joffe RT, Uhde TW, et al: Effects of carbamazepine on thyroid function in affectively ill patients: clinical and theoretical implications. *Arch Gen Psychiatry* 1984; 41:1150–1153
- Emerson CH, Dyson WL, Utiger RD: Serum thyrotropin and thyroxine concentrations in patients receiving lithium carbonate. *J Clin Endocrinol Metab* 1973; 36:338–346
- Post RM, Uhde TW, Ballenger JC, et al: Carbamazepine and its -10,11-epoxide metabolite in plasma and CSF: relationship to antidepressant response. *Arch Gen Psychiatry* 1983; 40:673–676
- Joffe RT: Hematological effects of lithium potentiation of carbamazepine in patients with affective illness. *Int Clin Psychopharmacol* 1988; 3:53–57
- Mastrosimone F, Capo G, Colucci D'Amato C: The use of lithium salts in trigeminal neuralgia in prevention of neutropenia due to carbamazepine: preliminary considerations. *Acta Neurol* 1979; 39:149–152
- Brewerton TD: Lithium counteracts carbamazepine-induced leukopenia while increasing its therapeutic effect. *Biol Psychiatry* 1986; 21:677–685
- Gallicchio VS, Hulette BC: *In vitro* effect of lithium on carbamazepine-induced inhibition of murine and human bone marrow-derived granulocyte-macrophage, erythroid, and megakaryocyte progenitor stem cells. *Proc Soc Exp Biol Med* 1989; 190:109–116
- Rossof AH, Fehir KM: Lithium stimulation of granulopoiesis (letter). *N Engl J Med* 1978; 298:280–281
- Rossof AH, Fehir KM: Lithium carbonate increases marrow granulocyte-committed colony-forming units and peripheral blood granulocytes in a canine model. *Exp Hematol* 1979; 7:255–258
- Stein RS, Hanson G, Kcethe S, et al: Lithium-induced granulocytosis. *Ann Intern Med* 1978; 88:809–810
- Gallicchio V, Chen MG: Modulation of murine pluripotent stem cell proliferation *in vivo* by lithium carbonate. *Blood* 1980; 56:1150–1152
- Gallicchio V, Chen MG: Influence of lithium on proliferation of hematopoietic stem cells. *Exp Hematol* 1981; 9:804–810
- Gallicchio VS, Gamba-Vitalo C, Watts TD, et al: *In vivo* and *in vitro* modulation of megakaryocytopoiesis and stromal colony formation by lithium. *J Lab Clin Med* 1986; 108:199–205
- Gallicchio VS: Lithium and granulopoiesis: mechanisms of lith-

- ium action, in *Lithium: Inorganic Pharmacology and Psychiatric Use*. Edited by Birch NJ. Oxford, England, IRL Press, 1988
27. Levitt LJ, Quesenberry PJ: The effect of lithium on murine hematopoiesis in a liquid culture system. *N Engl J Med* 1980; 302:713-719
28. Harker WG, Rosenstein G, Clarkson D, et al: Enhancement of colony-stimulating activity production by lithium. *Blood* 1977; 49:263-267
29. Richman CM, Kinnealey A, Hoffman PC: Granulopoietic effects of lithium on human bone marrow *in vitro*. *Exp Hematol* 1981; 9:449-455
30. Joffe RT, Kellner CH, Post RM, et al: Lithium increases platelet count (letter). *N Engl J Med* 1984; 311:674-675
31. Gamba-Vitalo C, Gallicchio VS, Watts TD, et al: Lithium stimulated *in vitro* megakaryocytopoiesis. *Exp Hematol* 1983; 11: 382-388
32. Bakker K: The influence of lithium carbonate on the hypothalamo-pituitary-thyroid axis: studies in patients with affective disorders, thyrotoxicosis, and hypothyroidism (MD thesis). Groningen, The Netherlands, State University of Groningen, 1977
33. De Luca F, Arrigo T, Pandullo E, et al: Changes in thyroid function tests induced by 2 month carbamazepine treatment in L-thyroxine-substituted hypothyroid children. *Eur J Pediatr* 1986; 145:77-79
34. Aanderud S, Myking OL, Strandjord RE: The influence of carbamazepine on thyroid hormones and thyroxine binding globulin in hypothyroid patients substituted with thyroxine. *Clin Endocrinol* 1981; 15:247-252
35. Joffe RT, Post RM, Ballenger JC, et al: The neuroendocrine effects of carbamazepine in patients with affective illness. *Epilepsia* 1986; 27:156-160
36. Larsen PR, Atkinson AJ, Wellmann HN, et al: The effect of diphenylhydantoin on thyroxine metabolism in man. *J Clin Invest* 1970; 49:1266-1279
37. Cullen MJ, Burger AG, Ingbar SH: Effects of diphenylhydantoin on peripheral thyroid hormone economy and the conversion of  $T_4$  to  $T_3$  (abstract). *Isr J Med Sci* 1972; 8:1968
38. Morselli PL, Biandrate P, Frigerio A, et al: Pharmacokinetics of carbamazepine in rats and humans. *Eur J Clin Invest* 1972; 2:297
39. Hesch RD, Brunner G, Soling HD: Conversion of thyroxine ( $T_4$ ) and triiodothyronine ( $T_3$ ) and the subcellular localisation of the converting enzyme. *Clin Chim Acta* 1975; 59:209-213
40. Visser TJ, Van der Does-IT, Docter R, et al: Subcellular localization of a rat liver enzyme converting thyroxine into triiodothyronine and possible involvement of essential thiol groups. *Biochem J* 1976; 157:479-482
41. Sedvall G, Jonsson B, Pettersson U, et al: Effects of lithium salts on plasma protein bound iodine and uptake of  $I^{131}$  in thyroid gland of man and rat. *Life Sci* 1968; 7:1257-1264
42. Berens SC, Bernstein AS, Robins J, et al: Antithyroid effects of lithium. *J Clin Invest* 1970; 49:1357-1367
43. Kendall-Taylor P: Comparison of the effects of various agents on thyroidal adenyl cyclase activity with their effects on thyroid hormone release. *J Endocrinol* 1972; 54:137-145
44. Wolff J, Berens SC, Jones AB: Inhibition of TSH-stimulated adenyl cyclase by low concentrations of lithium ion. *Biochem Biophys Res Commun* 1976; 73:383-390
45. Bagchi N, Brown TR, Mack RE: Studies on the mechanism of inhibition of thyroid function by lithium. *Biochim Biophys Acta* 1978; 542:163-169
46. Servant D, Danel T, Goudemand M: Lithium therapy in carbamazepine-induced agranulocytosis (letter). *Am J Psychiatry* 1988; 145:381
47. Joffe RT, Post RM: Lithium and carbamazepine-induced agranulocytosis (letter). *Am J Psychiatry* 1989; 146:404

# Response to Treatment With Antidepressants of Patients With Severe or Moderate Nonpsychotic Depression and of Patients With Psychotic Depression

James H. Kocsis, M.D., Jack L. Croughan, M.D.,  
Martin M. Katz, Ph.D., Thomas P. Butler, M.D., Steven Secunda, M.D.,  
Charles L. Bowden, M.D., and John M. Davis, M.D.

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*Hospitalized patients were divided into nonpsychotic severely depressed (N=53), nonpsychotic moderately depressed (N=54), and psychotic depressed (N=25) groups and treated with either imipramine or amitriptyline, up to 250 mg/day, for 4 weeks. Good response occurred in 39% of the 38 severely depressed, 67% of the 49 moderately depressed, and 32% of the 19 psychotic depressed patients who completed treatment. The response of the patients with nonpsychotic severe depression did not differ significantly from the response of those with psychotic depression, and both groups fared worse than the group with nonpsychotic moderate depression.*

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Reports of relatively poor response to treatment with tricyclic antidepressants (1, 2) have led to the widespread clinical practice in psychiatric inpatient settings of treating psychotic unipolar major depression with ECT or with a combination of tricyclics and antipsychotic drugs. It is not entirely clear whether the poor response to tricyclics of patients with psychotic major depression is a function of some qualitative difference associated with the psychotic state or of a more general refractoriness to treatment associated with more severe symptoms of depression (1, 3). Resolution of this issue has important implications for treatment selection. If severity alone accounts for poor response to treatment with tricyclics, then nonpsychotic severe major depression, which is operationally defined in the mood disorders section of *DSM-III-R*, might also require alternatives to treatment with tricyclics alone.

This report is based on results of reanalysis of treat-

ment response data from the National Institute of Mental Health (NIMH) Clinical Research Branch Collaborative Program on the Psychobiology of Depression. The depressed sample contained a large number of patients who had major depression without psychotic features. Thus, we were able to divide this group into severely depressed and moderately depressed subgroups. Response to tricyclic antidepressants could then be examined on the basis of severity of illness unconfounded by presence or absence of psychosis and could be compared to response in a separate psychotic depressed group. The hypothesis was that patients with nonpsychotic severe depression would respond to tricyclics as poorly as those with psychotic depression and that both of these groups would respond less favorably than the nonpsychotic moderately depressed group.

## METHOD

The design and rationale of the NIMH Clinical Research Branch Collaborative Program on the Psychobiology of Depression—Biological Studies have been described in detail (4-6). For the present study, hospitalized patients with diagnoses of depression were interviewed with the Schedule for Affective Disorders and Schizophrenia (SADS) (7) and were included if they met the Research Diagnostic Criteria (8) for major depressive disorder. Patients with unipolar depression, if they were under the age of 35, had to have had at least one prior depressive episode; if they were over age 35, no prior episodes were required. Patients who fulfilled criteria for schizoaffective disorders were excluded. This study was conducted in six U.S. hospital centers (see Acknowledgment). A total of 85 unipolar patients (39 male, 46 female) and 47 bipolar patients (31 male, 16 female) were studied.

Diagnosis of the psychotic subtype was derived from the SADS interview plus two SADS-C (9) interviews done by research psychiatrists during the first 2 weeks of the patients' hospitalizations but before initiation of antidepressant medication. Thus, any depressed pa-

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tient rated as having definite delusions and/or hallucinations at the time of the initial interview or as having possible delusions and/or hallucinations on the SADS, which were confirmed as definite by the subsequent SADS-C interviews, was included in the psychotic depressed group.

Training procedures for clinicians in the collaborating centers were held to establish and maintain interrater reliability. A method based on videotape recordings of brief interviews with a sample of representative patients was developed, and a cross-center reliability study was conducted. The kappa coefficients of the paired average ratings on the SADS of presence or absence of critical symptoms of depression such as delusions ranged from 0.63 to 0.92.

Severity of depressive illness was measured before and after treatment with tricyclics by means of the Hamilton Rating Scale for Depression (10) total score and the SADS-C global assessment scale. Assignment to the nonpsychotic severely depressed group or the nonpsychotic moderately depressed group was done according to a median split of the patients' day 10 Hamilton total scores (median score=26 for the nonpsychotic patients).

Ratings were made by research psychiatrists at the end of 4 weeks of treatment to determine treatment outcome. Hamilton depression scale and global assessment scale ratings were based on live interviews, while clinical global improvement and clinical global severity ratings were based on videotaped interviews (11). Patients were categorized as good responders, poor responders, or indeterminate responders on the basis of an algorithm derived from the four scales. The specific details have been published (4).

Days 1–14 of hospitalization constituted a drug-free placebo baseline period. Active treatment with amitriptyline or imipramine was double-blind; it was randomly assigned and began on day 15 according to the following schedule: days 15 and 16, 100 mg; days 17 and 18, 150 mg; days 19 and 20, 200 mg; days 21–41, 250 mg. Every effort was made to achieve the maximum dose. Twelve patients (eight taking amitriptyline and four taking imipramine) required treatment at lower doses because of side effects.

Analysis of variance was used to compare ages and scale scores across the three groups, and Duncan's multiple range test was used for pairwise comparisons. Chi-square analysis was used to test for differences in distribution of the sexes and outcome categories.

## RESULTS

One hundred thirty-two depressed patients were included in the study. Twenty-five were classified as psychotic (12 bipolar, 13 unipolar), and 107 as nonpsychotic (35 bipolar, 72 unipolar). On the basis of a median split of pretreatment Hamilton depression scores ( $N=107$ ; median score=26), the nonpsychotic patients were divided into severely depressed ( $N=53$ ;

13 bipolar, 40 unipolar) and moderately depressed ( $N=54$ ; 22 bipolar, 32 unipolar) subgroups. The distributions of the sexes and of the unipolar and bipolar subtypes were not significantly different among the three groups (severe, moderate, psychotic), although there was a trend toward a higher proportion of unipolar patients in the severely depressed group and a higher proportion of bipolar patients in the moderately depressed group.

The nonpsychotic severely depressed patients were found to be older than the other two groups. Severity of illness at baseline was about the same for the nonpsychotic severely depressed and the psychotic depressed groups; it was less for the nonpsychotic moderately depressed group. One hundred six patients completed 4 weeks of treatment with either amitriptyline or imipramine and could be classified as good, poor, or indeterminate responders. Higher, but not significantly different, dropout rates occurred in the nonpsychotic severely depressed and the psychotic depressed groups than in the nonpsychotic moderately depressed group. Response classifications did not differ significantly between the unipolar and bipolar subgroups or between the imipramine- and amitriptyline-treated subjects. The results are summarized in table 1.

Response to treatment with tricyclic antidepressants was significantly better for the nonpsychotic moderately depressed group. Sixty-seven percent of the 49 moderately depressed patients who completed 4 weeks of treatment were found to have a good outcome, compared to 39% of the 38 severely depressed and 32% of the 19 psychotic patients who completed treatment. Posttreatment scores on the Hamilton depression scale and the global assessment scale indicated less pathology in the nonpsychotic moderately depressed group than in the other two groups. Pairwise group comparisons revealed significant posttreatment differences among all groups on the Hamilton scale and for the psychotic group compared to the other two groups on the global assessment scale (see table 1). The final scores for the nonpsychotic severely depressed group were in between those of the psychotic depressed and nonpsychotic moderately depressed groups on both scales.

## DISCUSSION

There were two primary findings in this study. First, the outcome of 4 weeks of treatment with standard tricyclic antidepressants was better in a moderately depressed group of nonpsychotic hospitalized patients than in a severely depressed group. Second, the outcome for the nonpsychotic severely depressed group was intermediate between that of the patients with psychotic depression and that of the nonpsychotic moderately depressed group. Good outcome, defined as recovery or marked improvement, occurred in 67% of the moderately depressed, 39% of the severely de-

**TABLE 1. Response of Nonpsychotic Severely or Moderately Depressed Patients and Psychotic Depressed Patients to 4 Weeks of Treatment With Tricyclic Antidepressants**

Variable	Nonpsychotic Severely Depressed Patients (S) (N=53)				Nonpsychotic Moderately Depressed Patients (M) (N=54)				Psychotic Depressed Patients (P) (N=25)				Overall Comparison			Significant Pairwise Differences (p<0.05) <sup>a</sup>
	Mean	SD	N	%	Mean	SD	N	%	Mean	SD	N	%	F	df	p	
Age (years)	53	14	—	—	42	14	—	—	47	14	—	—	8.5	2, 129	0.003	S>M, S>P
Female sex	—	—	26	49	—	—	23	43	—	—	13	52	—	—	—	—
Bipolar disorder	—	—	13	25	—	—	22	41	—	—	12	48	—	—	—	—
Baseline Hamilton depression score	33	11	—	—	21	5	—	—	35	11	—	—	65.8	2, 127	0.0001	S>M, P>M
Baseline global assessment score	35	7	—	—	49	13	—	—	35	15	—	—	21.9	2, 127	0.0001	S<M, P<M
Dropouts	—	—	15	28	—	—	5	9	—	—	6	24	—	—	—	—
Plasma drug concentration (ng/ml)																
Amitriptyline	354	132	19	—	248	93	26	—	378	184	8	—	5.6	2, 50	0.006	S>M, P>M
Imipramine	257	107	16	—	301	199	18	—	361	184	8	—	1.1	2, 39	n.s.	—
Posttreatment Hamilton depression score	17	9	38	—	10	9	49	—	22	14	19	—	10.2	2, 105	0.0001	P>S, S>M, P>M
Posttreatment global assessment score	58	6	38	—	66	17	49	—	46	25	19	—	8.8	3, 105	0.0003	M>P, S>P
Response to drug <sup>b</sup>																
Good	—	—	15	39	—	—	33	67	—	—	6	32	—	—	—	—
Poor	—	—	10	26	—	—	8	16	—	—	9	47	—	—	—	—
Indeterminate	—	—	13	34	—	—	8	16	—	—	4	21	—	—	—	—

<sup>a</sup>Duncan's multiple range test.<sup>b</sup>Significant difference in response among the three groups ( $\chi^2=13.1$ ,  $df=4$ ,  $p=0.01$ ). Nonsignificant difference in response between severe and psychotic groups ( $\chi^2=2.6$ ,  $df=2$ , n.s.). Significant difference in response between severe and psychotic groups combined and moderate group ( $\chi^2=9.8$ ,  $df=2$ ,  $p=0.007$ ).

pressed, and 32% of the psychotic depressed patients who completed treatment.

Prior studies (1, 2) have clearly demonstrated a less favorable response of patients with psychotic unipolar major depression to treatment with tricyclic antidepressants when compared to patients with nonpsychotic depression. The only study that has directly addressed the contribution of psychotic state versus severity of illness to poor response to tricyclics is the Glassman et al. study (1), which divided a nonpsychotic sample on the basis of a median split of Hamilton depression scores. Nine patients scored above 27, and this group had a recovery rate of 56%. Twelve patients scored below 27, and 75% of these recovered. The authors interpreted this nonsignificant difference as evidence that psychosis rather than severity of illness alone accounted for the poor treatment response in the psychotic depressed group.

In the current study the nonpsychotic sample was divided according to the same method that Glassman et al. used, and the analysis led to different results. Our study suggests that nonpsychotic severely depressed patients respond more poorly to 4 weeks of treatment with standard tricyclics than do nonpsychotic moderately depressed patients.

This article reports an analysis of data from a study not originally designed to address the respective treatment responses of psychotic and nonpsychotic depressed patients. Several caveats must be mentioned in

considering the results. Prior reports of poor response to tricyclic antidepressants by patients with psychotic depression have focused mostly on those with unipolar depression. The current sample included both unipolar and bipolar depressed patients in the psychotic and the nonpsychotic groups. The small number of subjects did not permit meaningful analysis of the unipolar and bipolar subgroups separately. However, rates of good and poor response were equivalent in these two subgroups. Thus, it appeared that nonpsychotic severely depressed patients and psychotic depressed patients with bipolar depression responded unfavorably to treatment with tricyclics alone.

It should also be noted that for reasons unrelated to the current analysis, two different antidepressant drugs were used for treatment. Good, indeterminate, and poor responses were similar with imipramine and amitriptyline, but dividing the diagnostic groups by drug treatment resulted in small numbers in each subgroup.

Another important issue is that treatment with tricyclics lasted only 4 weeks. There were trends for more indeterminate outcomes and better posttreatment rating scores in the nonpsychotic severely depressed group than in the psychotic depressed group, which suggests that a higher rate of good response could have occurred in the severely ill group if there had been a longer duration of treatment. Unfortunately, the design of the current study did not include subsequent systematic treatments or follow-up. We do not know

what treatments were added or substituted after the unsuccessful 4 weeks of treatment with tricyclics. It is likely that many of these patients required ECT. Other possible treatments may have included longer trials of a tricyclic alone, addition of antipsychotic drugs or lithium, or other so-called "enhancing" techniques.

Despite these methodologic concerns, the results of the current data analysis are presented to alert clinicians to the possibility that patients with nonpsychotic severe major depression may respond less favorably than patients with nonpsychotic moderate depression to treatment with tricyclic antidepressants alone. Thus, alternative interventions may be needed in the treatment of the former group of patients. These results will require replication in a prospective study that uses a longer duration of treatment before implications become firmly accepted.

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#### REFERENCES

1. Glassman AH, Kantor SJ, Shostak M: Depression, delusions, and drug response. *Am J Psychiatry* 1975; 132:716-719
2. Brown RP, Frances A, Kocsis JH, et al: Psychotic vs nonpsychotic depression: comparison of treatment response. *J Nerv Ment Dis* 1982; 170:635-637
3. Bielski RJ, Friedel RO: Prediction of tricyclic antidepressant response: a critical review. *Arch Gen Psychiatry* 1976; 33: 1479-1489
4. Katz MM, Koslow SH, Berman N, et al: A multi-vantaged approach to measurement of behavioral and affect states for clinical and psychobiological research. *Psychol Rep* 1984; 55:619-671
5. Maas JW, Koslow SH, Davis JM, et al: Biological component of the NIMH Clinical Research Branch Collaborative Program on the Psychobiology of Depression, I: background and theoretical considerations. *Psychol Med* 1980; 10:759-776
6. Secunda S, Koslow SH, Redmond DE, et al: Biological component of the NIMH Clinical Research Branch Collaborative Program on the Psychobiology of Depression, II: methodology and data analysis. *Psychol Med* 1980; 10:777-793
7. Spitzer RL, Endicott J: Schedule for Affective Disorders and Schizophrenia (SADS), 3rd ed. New York, New York State Psychiatric Institute, Biometrics Research, 1977
8. Spitzer RL, Endicott J, Robins E: Research Diagnostic Criteria (RDC) for a Selected Group of Functional Disorders, 3rd ed. New York, New York State Psychiatric Institute, Biometrics Research, 1977
9. Spitzer RL, Endicott J: Schedule for Affective Disorders and Schizophrenia—Change Version (SADS-C). New York, New York State Psychiatric Institute, Biometrics Research, 1978
10. Hamilton M: A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960; 23:56-62
11. Katz MM, Itil TM: Video methodology for research in psychopathology and psychopharmacology. *Arch Gen Psychiatry* 1974; 31:204-210

# Diagnosis and Clinical Course of Erotomaniac and Other Delusional Patients

Marie Rudden, M.D., John Sweeney, Ph.D., and Allen Frances, M.D.

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*Twenty-eight patients with erotomaniac delusions were compared with 80 patients with other delusions to clarify questions about diagnosis and course of illness in erotomania. The erotomaniac patients were a heterogeneous group with respect to both diagnosis and course. They had significantly more manic symptoms than the comparison group and more affective diagnoses than would be expected from the literature; 25% (N=7) had schizoaffective disorder and 7% (N=2) had bipolar disorder. A subgroup of monodelusional erotomaniac patients was identified who met the DSM-III-R criteria for delusional disorder, thus supporting the decision to include erotomaniac delusions in this diagnostic category in the revision of DSM-III.*

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**E**rotomania—the delusional belief that one is passionately loved by another—has long been a symptom in search of adequate conceptualization and has been incorporated into diagnostic systems in many different ways. In the twentieth century, erotomaniac delusions have most often been related to paranoia (1). For example, modern American psychiatrists, such as Arieti (2), Hollender and Callahan (3), and Lehman (4), tended to classify patients with erotomaniac delusions as having paranoia if the delusions were the only psychotic symptom (primary erotomania) or as having paranoid schizophrenia if other psychotic symptoms were present (secondary erotomania). Other writers have argued for a more heterogeneous view of patients with erotomaniac delusions, however. Raskin and Sullivan (5) and Seeman (6), for instance, have pointed to cases in which the diagnoses of erotomaniac patients seemed to be those of affective or schizoaffective illnesses.

Some writers, especially in Europe (de Clerambault [7], Enoch et al. [8]), diagnosed primary erotomania as a monodelusional disorder in its own right. In particular, de Clerambault noted that patients with this dis-

order can be free of other symptoms of psychotic illness. Because of this he argued for erotomania's status as a discrete entity. Enoch et al. (8) described the outcomes of erotomaniac patients as variable: some go on to develop new symptoms of an ongoing psychotic process, while for others the outcome seems more favorable. Because of this heterogeneity, they proposed that a classification of erotomania with one group of psychotic illnesses or another is premature and argued for the retention of de Clerambault's syndrome as a nosological entity until the factors underlying this heterogeneity can be clarified further. An English group (9) also echoed this concern. *DSM-III* failed altogether to provide guidelines for the classification of erotomania. Strictly erotic delusions without persecutory content were not included in the criteria for paranoia. This omission probably stemmed from the conception of erotomania as a rare entity, usually listed under exotic syndromes and neglected in the recent literature.

This notion has been revised, however. Hollender and Callahan (3) observed that, given the number of patients with erotomaniac delusions which they found in a random inquiry, it was unlikely that erotomania was a rare occurrence. And in our previous study of delusional patients (10), delusions of erotomania were also found to be quite frequent (they were seen in 14% of the delusional women in the sample). A second reason for the absence of explicit diagnostic guidelines in *DSM-III* was, perhaps, the idea that patients with erotomaniac delusions could easily be given a diagnosis of some other psychotic disorder such as mania or schizophrenia, but this leaves the diagnoses of many primary erotomaniac patients in question. Partly on the basis of our discussion of these issues in a previous article (11), *DSM-III-R* includes erotomaniac delusions among the criteria for delusional disorder.

Just as the literature is unresolved about the diagnosis of erotomania, so too is it unclear about the course. Most writers generally conclude that this is a chronic illness, relatively refractory to treatment (2, 3, 12). However, notable exceptions have been mentioned by Raskin and Sullivan (5), Enoch et al. (8), and Seeman (6), who described one group of women with erotomaniac delusions who were chronically delusional and functioned at a low level but also another group of women with higher functioning and a less malignant course which resembled that of affective disorders.

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The literature on erotomania has been characterized by limited research data—small studies and lack of systematic description, assessment, and diagnosis. To develop a more empirical description of patients with erotomaniac delusions, we collected data on a group of 28 patients with these delusions (the largest sample that has been reported on to date). The patients were given diagnoses according to *DSM-III-R* criteria and were compared with a group of nonerotomaniac delusional patients. We were particularly interested in studying descriptive, course, and family history variables relevant to the validation of the diagnostic classification of erotomaniac patients.

## METHOD

During the past 6 years, we collected data on 28 patients with erotomaniac delusions who were inpatients or outpatients under treatment at the Payne Whitney Clinic. Since referrals to the study were made only by staff members who were aware of our interest, the sample probably did not include every patient with erotomania treated in the hospital during that period. Nine patients were treated by us personally for varying lengths of time (from 1 month to 4 years). Information on the other patients was obtained by systematic chart review, videotaped interviews, and discussions with therapists about relevant diagnostic and treatment issues. All of the erotomaniac patients were studied systematically on a number of demographic and clinical course variables: age, sex, marital status, race, social class, and household size; presence or absence of other delusions, hallucinations, thought disorder, flat affect, or bizarre behavior; acuteness of onset of the delusional episode; presence or absence of deterioration in social adjustment; number of *DSM-III* symptoms of depression and of mania; diagnosis; medications used, compliance with treatment, and response to treatment; and family history of affective disorder, alcoholism, or schizophrenia. Six of the erotomaniac patients were followed for up to 5 years; information from them about changes in symptoms or diagnoses is presented.

The erotomaniac patients were compared with a group of delusional patients, described previously (10), who had come consecutively to the Payne Whitney Clinic in 1980–1981 for treatment and were studied at that time by examination of the same variables in chart review. That study, beginning with 100 delusional patients, excluded patients who had primary organic diagnoses, who were older than 65, or for whom adequate information for determining diagnosis could not be obtained from chart review. This left a study group of 88 patients, 44 men and 44 women. Eight of these patients (six women and two men) had erotomaniac delusions and were thus excluded from the present comparison group, leaving a comparison sample of 80 delusional patients.

**TABLE 1. Characteristics of Erotomaniac Patients and Patients With Other Delusions**

Variable	Erotomaniac Patients (N=28)		Patients With Other Delusions (N=80)	
	N	%	N	%
Female sex <sup>a</sup>	21	75	38	48
Marital status				
Never married	19	68	52	65
Married	5	18	18	23
Divorced/widowed	4	14	10	13
Symptom				
Auditory hallucinations	11	39	33	41
Bizarre behavior	13	46	40	50
Thought disorder	11	39	41	51
Flat affect	5	18	27	34
Deterioration in functioning	15	54	43	54
Medication				
Neuroleptic	21	75	68	85
Lithium <sup>b</sup>	9	32	9	11
Antidepressant	9	32	10	13
Family history <sup>c</sup>				
Schizophrenia	3	14	20	32
Affective disorder	7	33	20	32
Alcoholism	3	14	9	15
Diagnosis				
Schizophrenia or schizophreniform disorder	12	43	46	58
Affective disorder, bipolar	2	7	14	18
Paranoid or delusional disorder	7	25	9	11
Other (e.g., schizoaffective disorder)	7	25	11	14

<sup>a</sup>Significant difference between groups ( $\chi^2=5.27$ ,  $df=1$ ,  $p<0.03$ ).

<sup>b</sup>Significant difference between groups ( $\chi^2=5.10$ ,  $df=1$ ,  $p<0.03$ ).

<sup>c</sup>Data were available for 21 erotomaniac patients and 62 patients with other delusions; percents are based on the number of patients for whom data were available.

## RESULTS

The erotomaniac sample included seven men and 21 women 18 to 63 years old (mean  $\pm$  SD =  $31.6 \pm 9.9$  years). The delusional group contained 42 men and 38 women whose mean age was  $31.8 \pm 10.8$  years. The socioeconomic status of both groups varied widely from social class I to V; the mean was class III. Most of the subjects in the two groups were unmarried. The demographics in the erotomaniac group and the general delusional group differed significantly only in the distribution of the sexes (see table 1). There were no statistical differences in age, race, social class, household size, or marital status.

There was diagnostic heterogeneity among the erotomaniac patients (see table 1). Two patients, apart from having diagnoses of delusional disorder, had additional diagnoses of major depression at one point during the course of treatment, and another had a diagnosis of atypical affective disorder.

The group of patients with erotomaniac delusions

was similar to the larger delusional group on most variables besides the demographic ones, including diagnosis, the presence or absence of additional symptoms of psychopathology, deterioration in course, use of or response to somatic therapies, and compliance with treatment. However, the erotomanic group had a significantly higher number of *DSM-III* manic symptoms ( $\text{mean} \pm \text{SD} = 3.0 \pm 2.2$ ) than the group of delusional patients ( $1.9 \pm 2.2$ ) ( $t = 2.31$ ,  $df = 106$ ,  $p < 0.03$ ). There were no significant differences in other affective features, such as the  $\text{mean} \pm \text{SD}$  number of symptoms of depression (erotomanic group,  $2.9 \pm 1.9$ ; delusional group,  $2.7 \pm 2.2$ ) or diagnosis. However, significantly more erotomanic patients than comparison patients were treated with lithium (see table 1).

Erotomanic and comparison patients had similar percentages of first- or second-degree relatives with alcoholism and affective illness, but the erotomanic patients had a lower percentage of relatives with schizophrenia (see table 1).

The clinical course of the erotomanic patients was varied and only sometimes approximated the chronically refractory picture described in much of the literature. Course seemed to vary most with diagnosis: the schizophrenic erotomanic patients, as might be expected, did least well in terms of chronicity, rehospitalization, functional deterioration, etc. Some schizoaffective patients had an intermediate course, with occasional rehospitalizations or somewhat diminished social functioning. The patients with diagnoses of delusional disorder were among those with the highest level of functioning. Although three of these patients were chronically delusional for long periods (2, 10, and 24 years), only one ever required hospitalization, and she had demonstrated superior intellectual and occupational functioning during the 23 years before her hospitalization, during which time she remained quietly delusional about the same man. Of the four women with briefer episodes of delusional disorder (lasting 1–6 months), three had superior occupational functioning, and two were free of any recurrent delusions after a 3-year follow-up period. A third had a 1-week episode of paranoid delusions about an actual lover, and the fourth had a recurrent erotomanic delusion about her therapist.

## DISCUSSION

The data produced several new findings. First, the erotomanic patients were a heterogeneous group with a variety of diagnoses that fell primarily into the categories of delusional disorder, schizophrenia, or schizoaffective disorder, manic type. This finding differs from much of the literature, which describes erotomanic patients as usually fitting into the first two of these diagnostic categories and pays little attention to affective symptoms or diagnoses. In fact, however, the disorders of 25% of these patients had striking affective features,

contributing to the schizoaffective diagnoses, and 7% of the patients had bipolar disorder. In addition, the erotomanic group as a whole had more manic symptoms than did the general delusional group. (This was accounted for by a variety of manic symptoms and not by hypersexuality alone.) A larger proportion of the erotomanic patients were also treated with lithium. A possibly related finding was the tendency for the erotomanic patients to have fewer first- or second-degree relatives with schizophrenia, although the two groups of patients had similar percentages of relatives with affective disorders.

Further, despite the general heterogeneity in diagnosis, a subgroup of patients ( $N = 7$ ), each of whom had only one delusion and no other psychotic symptoms, was identified. With *DSM-III-R*, all of these patients could be given diagnoses of delusional (paranoid) disorder. They had a generally better clinical course than the other patients, with far fewer hospitalizations and no further accrual of symptoms over fairly long periods of time. (This information was obtained by history from the three very chronically delusional women and by follow-up of three of the four more briefly delusional erotomanic patients.) These women's histories are thus similar to the descriptions of course and degree of impairment in delusional disorder both in *DSM-III-R* and in Winokur's 1977 study on this diagnosis (13). These findings therefore seem to emphasize the value of the revised version of *DSM-III*, which includes erotomania as one type of delusional disorder.

Finally, the course of illness in patients with erotomanic delusions was not so uniform as much of the literature would suggest. While all of the patients did not have a chronic, refractory course, neither were they exactly like Seeman's group (6), in which chronicity seemed linked to a low level of functioning but in which there was a subgroup of acutely ill patients with recurrent symptoms, a higher level of social functioning, and a better overall prognosis. In our sample, one of the most chronically delusional patients (a woman whose delusion had lasted 24 years) was highly successful in her profession. The women who had briefer periods of erotomanic delusions also functioned at a higher level, and so far only one has developed a recurrence of erotomanic delusions after a follow-up period of several years.

In summary, our study suggests that erotomanic symptoms in themselves do not predict either diagnosis or clinical course. We did identify a larger number of accompanying affective symptoms and a greater number of affective diagnoses, however, than have been traditionally described for erotomanic patients. Thus, clinicians might well look for these symptoms when considering the diagnosis and treatment of a patient with erotomania. Our clinical study also identified a subgroup of erotomanic patients with an apparent monodelusional disorder and good prognosis. This subgroup of erotomania seems to be best conceptualized as a type of delusional disorder. We hope that placement of erotomania

in this category, as was done in *DSM-III-R*, will be continued in future diagnostic systems.

# REFERENCES

1. Kraepelin E: Manic-Depressive Insanity and Paranoia. Translated by Barclay RM; edited by Robertson GM. Edinburgh, E & S Livingstone, 1921, p 245
2. Arieti S (ed): American Handbook of Psychiatry, 1st ed, vol I. New York, Basic Books, 1959, pp 525, 551
3. Hollender MH, Callahan AS III: Erotomania or de Clerambault syndrome. Arch Gen Psychiatry 1975; 32:1574-1576
4. Freedman AM, Kaplan HI (eds): Comprehensive Textbook of Psychiatry, 1st ed. Baltimore, Williams & Wilkins, 1967, p 1155
5. Raskin DE, Sullivan KE: Erotomania. Am J Psychiatry 1974; 131:1033-1035
6. Seeman MV: Delusional loving. Arch Gen Psychiatry 1978; 35: 1265-1267
7. de Clerambault GG: Les psychoses passionnelles, in Oeuvre psychiatrique. Paris, Presses Universitaires de France, 1942
8. Enoch MD, Trethowan WH, Banker JE: Some Uncommon Psychiatric Syndromes. Bristol, England, John Wright & Sons, 1967
9. Taylor P, Mahendra B, Gunn J: Erotomania in males. Psychol Med 1983; 13:645-650
10. Rudden M, Sweeney J, Frances A, et al: A comparison of delusional disorders in women and men. Am J Psychiatry 1983; 140:1575-1578
11. Rudden M, Gilmore M, Frances A: Erotomania: a separate entity. Am J Psychiatry 1980; 137:1262-1263
12. Goldstein RL: What is de Clerambault's syndrome? Harvard Medical School Mental Health Letter 1987; 3(12):8
13. Winokur G: Delusional disorder. Compr Psychiatry 1977; 18: 511-521

# Reduced Dark-Adaptation: An Indication of Lithium's Neuronal Action in Humans

Hinderk M. Emrich, M.D., Josef Zihl, Ph.D., Costas Raptis, M.D., and Anna Wendl

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*Although lithium plays a major role in therapy and prophylaxis of affective psychoses, no direct indication of its neuronal action in humans exists. A lithium-induced strong reduction of foveal dark-adaptation was found in healthy volunteers, and a lithium-induced reduction was also measured in patients with affective psychoses. Dark-adaptation measurements apparently offer the opportunity for in vivo monitoring of lithium's CNS effects in humans and may predict lithium's clinical efficacy.*

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Lithium exerts a great variety of biochemical, biophysical, and pharmacological actions (1), and it is an open question as to which of them is therapeutically relevant in affective illness. A great advantage would be gained if a clinically applicable neurobiological effect of lithium could be measured. Lithium induces an increase in intraneuronal calcium (2), which exerts a coupling between photo-bleaching of rhodopsin and the generation of receptor potentials within the photoreceptor cells (3); on the basis of this, it has been hypothesized that lithium impairs visual function, especially dark-adaptation. Results of experiments using the Arden ratio of electro-oculography as an indirect indicator of dark-adaptation were in line with this hypothesis (4, 5).

In the present study, foveal dark-adaptation was directly measured in normal volunteers before, during, and after lithium administration, as well as in lithium-treated patients suffering from an affective psychosis.

## METHOD

Fifteen healthy volunteers (age range=20-44 years, mean $\pm$ SD=27.5 $\pm$ 8.4 years) received lithium, administered orally, for 10-19 days. Lithium levels were adjusted to therapeutic levels (range=0.4-0.8 meq/liter,

mean $\pm$ SD=0.67 $\pm$ 0.12 meq/liter). We also studied 30 patients suffering from an affective or schizoaffective psychosis. Their DSM-III diagnoses were schizophrenia, paranoid (N=1) and schizoaffective (N=9) types; manic disorder, recurrent episode (N=5); and bipolar affective disorder, manic (N=8) and depressed (N=7). These patients were on a continuous lithium regimen (lithium levels=0.4-1.1 meq/liter, mean $\pm$ SD=0.64 $\pm$ 0.16 meq/liter) and were studied during a symptom-free interval. Written informed consent was obtained from patients and volunteers, and the study was reviewed and accepted by the ethical committee of the institute.

Light- and dark-adaptation were measured with a Tübinger perimeter (6) by determination of the luminance-difference thresholds in the visual field, according to the method of Aulhorn and Harms (7). According to Shapley and Enroth-Cugell (8), photopic adaptation is defined as the variation in sensitivity to light due to an increase in background illumination, whereas scotopic adaptation refers to the recovery of sensitivity in the dark. A white test spot (diameter=116 minutes of arc) was presented foveally for 0.5 seconds. Light difference threshold was determined by using the ascending method of limits (luminance steps=0.1 log units) at background luminance levels of 320 cd/m<sup>2</sup> for photopic vision and 0.00032 cd/m<sup>2</sup> for scotopic vision. Intervals between threshold measurements were 1 minute in the photopic and 2 minutes in the scotopic adaptation conditions. Adaptation times were 10 minutes for the photopic condition and 20 minutes for the scotopic condition. The criterion for light difference threshold was correct detection of the target in four consecutive trials.

## RESULTS

Figure 1 gives an example of a measurement of dark-adaptation monitoring the time course of increase in scotopic foveal sensitivity in a normal proband before and during lithium treatment. A strong lithium-induced reduction in foveal sensitivity can be observed. The dark-adaptation data, documented in figure 2, reveal the increases in foveal sensitivity in volunteers and patients that were reached during a time course of 20 minutes. In the 15 healthy volunteers, dark-adaptation

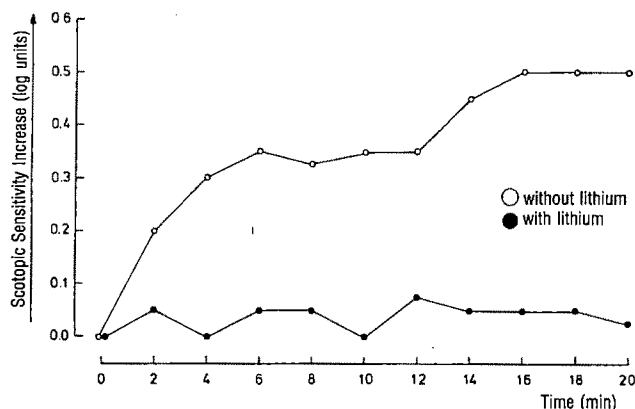
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**FIGURE 1.** Increase in Scotopic Foveal Sensitivity (Dark-Adaptation) as a Function of Time in a Healthy Volunteer Before and During Lithium Treatment

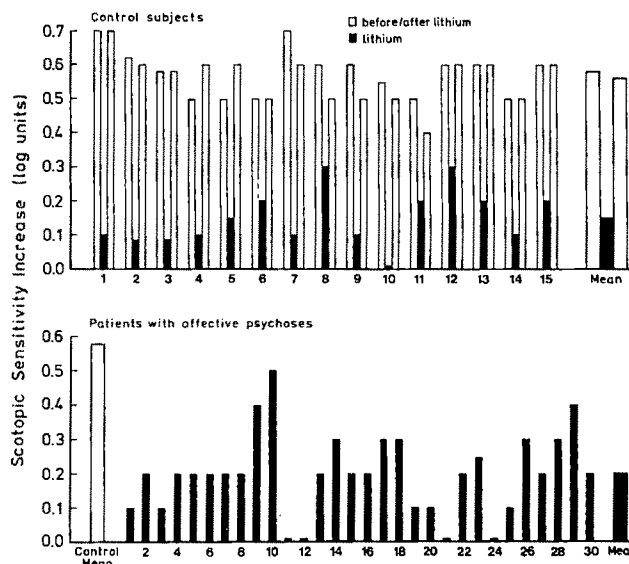


ranged from 0.50 to 0.72 log units (mean $\pm$ SD=0.58 $\pm$ 0.07) before lithium administration and was reduced during lithium administration to 0.02 to 0.30 log units (mean $\pm$ SD=0.15 $\pm$ 0.08) (figure 2). After discontinuation of lithium treatment the values returned to approximately initial levels. The difference between pre-lithium and lithium conditions was significant at the 0.01 level (Wilcoxon test for paired differences, two-tailed). In addition, the difference between lithium and postlithium conditions was highly significant ( $p < 0.001$ , Wilcoxon test, two-tailed). The analysis of variance with repeated measures also yielded a highly significant difference between prelithium, lithium, and postlithium conditions (Wilks's lambda=0.05, approximate  $F=117.61$ ,  $df=2, 13$ ,  $p < 0.00005$ ).

In contrast to these findings, light-adaptation was practically unchanged by lithium (data not shown). In the 30 patients suffering from an affective psychosis, the dark-adaptation values with lithium prophylaxis were very low, ranging from 0.02 to 0.50 log units (mean $\pm$ SD=0.20 $\pm$ 0.12) (figure 2). There was no statistically significant difference between the mean dark-adaptation values with lithium in affectively ill patients and the lithium-induced values of the control subjects. One patient (patient 9) exhibited normal dark-adaptation and was clinically demonstrated to be a nonresponder to lithium. In similar cases (patients 10 and 29), the prophylactic effect of lithium could not be evaluated because the lithium regimen had to be discontinued due to side effects. Most of the patients exhibited low dark-adaptation with lithium and clinically were partial responders or responders. However, lithium's prophylactic efficacy in patient 24 could not be evaluated because the therapeutic observation period was too short.

For most of the patients, the nonlithium condition could not be evaluated for ethical reasons, since the risk of a relapse of the disorder is high after lithium discontinuation. However, in a subgroup of seven affectively ill patients, dark-adaptation could be measured before and during lithium treatment. The prelith-

**FIGURE 2.** Increase in Scotopic Foveal Sensitivity (Dark-Adaptation) Within 20 Minutes in 15 Healthy Volunteers Who Were Treated With Lithium for 10–19 Days and in 30 Patients With Affective Psychoses Who Were Treated With Lithium



ium dark-adaptation ranged from 0.50 to 0.80 log units (mean $\pm$ SD=0.59 $\pm$ 0.13), and the dark-adaptation values during the lithium regimen ranged from 0.02 to 0.40 log units (mean $\pm$ SD=0.21 $\pm$ 0.13). This difference was significant ( $p < 0.001$ , Wilcoxon test, two-tailed). Carbamazepine, which is an alternative to lithium in the prophylaxis of affective disorders (9), had no influence on dark-adaptation in six patients (range=0.40–0.70 log units, mean $\pm$ SD=0.52 $\pm$ 0.10).

## DISCUSSION

The observed highly significant reduction of foveal dark-adaptation during lithium treatment of normal volunteers and the finding that patients suffering from affective psychoses also have low dark-adaptation values during lithium prophylaxis demonstrate that foveal dark-adaptation apparently is a direct indicator of lithium's neuronal action within a part of the human CNS. This finding is in line with results demonstrating a lithium-induced retinal injury in rats (10). The mode of action of this effect is unknown but may be related to lithium's influence on intracellular calcium, possibly due to its action on inositol-3-phosphate, which exerts calcium-releasing effects (11). Lithium's action on cyclic guanosine monophosphate (cGMP) must also be taken into account, since cGMP is also an important intracellular mediator of photoelectrogenesis (12); recently, lithium's effect on GTP binding has been demonstrated to be of pharmacological importance in the therapy of affective disorders (13).

Clinically, the lithium-induced reduction of foveal dark-adaptation may be regarded as an important

functional indicator, at the CNS level, of the activity of this mood stabilizer. However, further studies are required to determine whether foveal dark-adaptation represents a predictor of lithium's clinical efficacy. The data accumulated to date are not at variance with this hypothesis; nor is the lack of efficacy of carbamazepine on dark-adaptation contradictory, since carbamazepine probably exerts its antimanic action through another mode of action (e.g., reduction of glutamate release [M. Schmutz, personal communication]). From a practical point of view, lithium-induced reduction of dark-adaptation apparently has only minor importance in driving a car, since in the dark the extrafoveal mechanisms (rod-photoreception), which are not influenced by lithium, are of relevance. Mesopic vision, however, may be impaired by lithium; there have been anecdotal reports of this phenomenon, and their possible relevance should carefully be examined in the future.

#### REFERENCES

1. Johnson FN (ed): Handbook of Lithium Therapy. Baltimore, University Park Press, 1980
2. Aldenhoff JB, Lux HD: Measurement of Steady State and Transient Changes of Intracellular Calcium in Snail Neurons Under Lithium-Chloride. *Pflugers Arch* (suppl) 1980; R19
3. Yoshikami S, George JS, Hagins WA: Light-induced calcium fluxes from outer segment layer of vertebrate retinas. *Nature* 1980; 286:395-398
4. Emrich HM, Ullrich A, Adamczyk J, et al: Lithium affects EOG in humans (letter). *Psychiatry Res* 1984; 13:355-357
5. Ullrich A, Adamczyk J, Zihl J, et al: Lithium effects on ophthalmological-electrophysiological parameters in young healthy volunteers. *Acta Psychiatr Scand* 1985; 72:113-119
6. Sloan LL: The Tübinger perimeter of Aulhorn and Harms. *Arch Ophthalmol* 1971; 86:612-622
7. Aulhorn E, Harms H: Visual perimetry, in *Handbook of Sensory Physiology*, vol VII/4: Visual Psychophysics. Edited by Jameson D, Hurvich L. Berlin, Springer-Verlag, 1972
8. Shapley R, Enroth-Cugell C: Visual adaptation and retinal gain control. *Prog Retinal Res* 1984; 3:263-346
9. Emrich HM, Okuma T, Müller AA (eds): Anticonvulsants, in *Affective Disorders*. Amsterdam, Excerpta Medica, 1984
10. Remé C, Federspiel E, Pfeilschifter J, et al: Potentiation by light of lithium-induced retinal injury in rats (letter). *N Engl J Med* 1987; 317:1478
11. Berridge MJ, Irvine RF: Inositol trisphosphate, a novel second messenger in cellular signal transduction. *Nature* 1984; 312:315-321
12. Fein A, Payne R, Corson DW, et al: Photoreceptor excitation and adaptation by inositol 1,4,5-trisphosphate. *Nature* 1984; 311:157-160
13. Avissar S, Schreiber G, Danon A, et al: Lithium inhibits adrenergic and cholinergic increases in GTP binding in rat cortex. *Nature* 1988; 331:440-442

# Sexual and Physical Abuse Histories and Psychiatric Symptoms Among Male Psychiatric Outpatients

Chester Swett, Jr., M.D., Janet Surrey, Ph.D., and Caryn Cohen, B.A.

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*Of 125 consecutive male patients at an adult psychiatric outpatient clinic, 48% reported histories of sexual abuse and/or physical abuse. The mean scores on the global severity index of the SCL-90-R at the first visit were significantly higher for those who reported histories of abuse than for those who had no such history. Childhood abuse also was associated with high levels of psychiatric symptoms in these men.*

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Work by Bryer et al. (1) revealed a high rate of reported histories of abuse among women who had been psychiatrically hospitalized. Higher levels of current symptoms also were reported by those with histories of childhood abuse than by those who reported no such history. Our (unpublished) studies of female outpatients indicated that high levels of reported abuse are associated with high levels of current symptoms. Abuse is an unidentified component of the psychopathology of many women who are difficult to assess and treat (1-4). Histories of abuse among men may be nearly as prevalent (5-9). We studied new male patients in an adult psychiatric outpatient clinic to determine the rate of reported history of abuse and the relationship between history of abuse and current severity of symptoms. It was hypothesized that there would be a high level of abuse among these men and a higher level of symptoms among abused men than among nonabused men.

## METHOD

The study was conducted in a psychiatric outpatient clinic for adults that offers scheduled appointments for evaluation and treatment with a spectrum of modalities,

including individual psychotherapy and pharmacotherapy. However, there is no walk-in service, no crisis management program, and no special service for abused patients.

A self-rating packet of clinically relevant background questions was completed routinely on a voluntary basis by each of 145 of 158 consecutive men at the time of his first appointment. A total of 125 men provided data sets sufficiently complete to permit analysis. Most patients were unmarried, Caucasian, employed or in college, and Roman Catholic. Most had at least some postsecondary education. Their mean  $\pm$  SD age was  $37.1 \pm 12.4$  years.

The data included demographic information and scores on the SCL-90-R normalized for outpatients (10). A DSM-III-R diagnosis was given to each patient after the first assessment interview by a clinician without knowledge of the information contained in the self-rating packet.

The packet included questions about whether the patient ever had experienced physical or sexual abuse. There was an assurance that the resident was available to discuss any issues that might arise as a result of answering the questions. The question regarding physical abuse was "Have you ever been physically hurt or attacked by someone—such as wife, parent, another family member, or friend (for example, have you ever been kicked, bitten, pushed, or otherwise physically hurt by someone)?"

The question about sexual abuse was "Have you ever been pressured into doing more sexually than you wanted to do or were too young to understand? (By sexually we mean being pressured against your will into forced contact with the sexual part of your body or his/her body.)"

If a patient answered in the affirmative to either of the questions on physical abuse and sexual abuse, then information was obtained on age at the first episode of abuse, age at most recent abuse, number of episodes of abuse, and relationship of abuser to the abused. Early abuse was defined as abuse before age 18 years; later abuse was defined as that occurring at age 18 or after.

The therapists of a subsample of 34 consecutive patients, either abused or nonabused, were contacted to obtain further information on axis II diagnoses and to determine whether the patients' histories of abuse were discussed in therapy.

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Received March 28, 1989; revision received Oct. 4, 1989; accepted Nov. 8, 1989. From the Department of Psychiatry, Harvard Medical School and McLean Hospital, Belmont, Mass. Address reprint requests to Dr. Swett, Dartmouth Medical School and Brattleboro Retreat, 75 Linden St., Box 803, Brattleboro, VT 05302.

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Data analysis consisted of deriving descriptive statistics and mean $\pm$ SD values for the SCL-90-R scores and then performing *t* tests, Pearson product-moment correlations, and chi-square tests (Yates corrected if applicable). Analyses of variance (ANOVAs) were then carried out with the four mutually exclusive categories of physical abuse, sexual abuse, both physical abuse and sexual abuse, and no history of abuse. The Bonferroni correction for multiple comparisons was used to determine statistical significance in the one-way ANOVAs. The SCL-90-R scores at admission were used for multicollinearity and principal components analyses (11). Then histories of physical and sexual abuse were used in a stepwise multiple regression analysis to predict scores on the SCL-90-R completed at the time of admission. Finally, a probit regression analysis (12) was carried out to predict which patients had histories of abuse.

## RESULTS

### *Rates of Abuse*

Of the 125 new male outpatients who completed the self-rating packet, 60 (48%) reported histories of abuse at some time in their lives. Nine (7%) reported sexual abuse only, 44 (35%) reported physical abuse only, seven (6%) reported both types of abuse, and 65 (52%) reported no history of abuse.

Of the 53 men for whom age at first abuse was known, 45 (85%) reported that the first episode of abuse was before age 18. Seven (13%) reported sexual abuse only, 34 (64%) reported physical abuse only, and four (8%) reported both types of abuse.

None of the seven patients reporting early sexual abuse also reported later sexual abuse, but nine (26%) of the 34 patients reporting early physical abuse reported later physical abuse. Four (57%) of the seven patients with known age at both types of abuse reported both early and later abuse.

### *Relationship Between Victim and First Abuser*

The nine patients with histories of sexual abuse only reported on their relationships to the abusers. The abuser was a friend in two cases, a brother, uncle, authority figure, other person, or stranger in one case each, and some other family member in two cases.

Forty-three of the 44 patients who reported physical abuse only reported on their relationships to the abusers. The abusers were fathers (N=14), brothers (N=8), mothers (N=6), strangers (N=6), friends (N=3), spouses (N=2), another family member (N=1), an uncle (N=1), a sister (N=1), and an authority figure (N=1).

Five of the seven patients with histories of both types of abuse reported the abusers' relationships to them:

father (N=3), another family member (N=1), and other person (N=1).

### *Abuse and Adult Psychiatric Symptoms*

According to a one-way ANOVA, there were significant differences in SCL-90-R global severity indexes (total scores) of the patients in the four abuse categories ( $F=8.36$ ,  $df=3$ , 121,  $p<0.0009$ ). The mean $\pm$ SD values for those with histories of both physical abuse and sexual abuse ( $55.1\pm8.1$ ), physical abuse only ( $51.8\pm10.9$ ), and sexual abuse only ( $57.8\pm11.6$ ) were higher than that of the patients with no reported history of abuse ( $44.3\pm10.1$ ).

Table 1 contains each group's scores on the subscales of the SCL-90-R. The scores on four subscales and the global severity index showed statistically significant differences among the four groups after use of the Bonferroni correction for multiple comparisons. The other five subscales showed trends toward significance. The lowest mean scores on all subscales were for the patients who did not report histories of abuse. The highest mean scores were always for those with histories of sexual abuse only or both types of abuse.

Abuse during the year before the clinic visit was reported by only two of the patients with histories of physical abuse and by none of those with histories of sexual abuse. The scores of those two patients were similar to the mean scores of the other patients with histories of physical abuse.

The results of a one-way ANOVA on the global severity indexes of the patients who had experienced abuse before the age of 18 years showed statistically significant differences among the four abuse groups ( $F=8.00$ ,  $df=3$ , 106,  $p<0.0009$ ). The mean scores of the patients with histories of both types of abuse ( $57.8\pm9.0$ ), physical abuse only ( $52.7\pm10.6$ ), and sexual abuse only ( $56.9\pm12.5$ ) were higher than the score of the patients who reported no history of abuse ( $44.3\pm10.1$ ).

The data in table 1 show that the patients reporting histories of early abuse had statistically significantly higher scores on five of the subscales and the global severity index (with the Bonferroni correction). There were trends toward significance in the data on the other four subscales.

We also identified 32 patients who reported that the first episode of abuse occurred before the age of 12 years. Three of these patients reported both types of abuse, 26 reported physical abuse only, and three reported sexual abuse only. A one-way ANOVA showed the same trends toward higher SCL-90-R scores for those who reported abuse before age 12 than for the 65 patients with no reported history of abuse. Statistically significant differences (with the Bonferroni correction for multiple comparisons) were again shown for somatization ( $F=4.70$ ,  $df=3$ , 93,  $p<0.005$ ), psychoticism ( $F=5.31$ ,  $df=3$ , 93,  $p<0.002$ ), and the global severity index ( $F=5.57$ ,  $df=3$ , 93,  $p<0.002$ ).

The patients who reported first abuse before the age



**TABLE 1. SCL-90-R Scores of 125 Male Psychiatric Outpatients Reporting Histories of Physical Abuse, Sexual Abuse, Both Types of Abuse, or No Abuse**

SCL-90-R Scale	Score								One-Way ANOVA <sup>a</sup>	
	Both Types of Abuse		Physical Abuse Only		Sexual Abuse Only		No Abuse			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	p
All patients <sup>b</sup>										
Somatization	53.7	9.5	53.2	10.9	55.0	10.1	47.1	9.2	4.41	0.006
Obsessive-compulsive	54.1	5.6	50.5	8.8	52.7	10.4	46.1	10.2	3.40	0.02
Interpersonal sensitivity	53.6	6.8	51.6	8.4	56.6	9.3	45.4	11.0	6.11	0.001 <sup>c</sup>
Depression	54.9	7.4	51.0	10.5	58.1	10.7	45.6	10.1	6.18	0.001 <sup>c</sup>
Anxiety	55.1	7.1	50.3	12.5	57.2	7.9	43.2	9.9	8.16	0.0009 <sup>c</sup>
Hostility	55.0	4.6	51.4	10.4	53.8	6.7	47.4	10.9	2.62	0.05
Phobia	54.9	8.6	50.4	10.7	55.2	12.1	45.9	9.2	4.32	0.007
Paranoid	52.4	9.2	50.7	9.9	55.3	8.9	46.6	9.5	3.42	0.02
Psychoticism	55.7	10.8	51.0	11.0	59.0	14.6	44.6	10.9	6.99	0.0009 <sup>c</sup>
Global severity index	55.1	8.1	51.8	10.9	57.8	11.6	44.3	10.1	8.36	0.0009 <sup>c</sup>
Abuse before age 18 <sup>d</sup>										
Somatization	56.5	9.7	54.8	10.2	54.7	11.3	47.1	9.2	5.84	0.001 <sup>c</sup>
Obsessive-compulsive	52.8	6.9	50.7	8.3	54.4	7.5	46.1	10.2	3.17	0.03
Interpersonal sensitivity	56.3	6.0	52.1	8.2	55.3	9.8	45.4	11.0	5.40	0.002 <sup>c</sup>
Depression	57.3	9.4	50.8	9.5	56.6	11.2	45.6	10.1	4.95	0.003 <sup>c</sup>
Anxiety	56.8	8.2	51.3	12.3	56.1	8.5	43.2	9.9	7.49	0.0009 <sup>c</sup>
Hostility	57.0	5.4	52.3	10.8	54.7	7.2	47.4	10.9	2.91	0.04
Phobia	55.8	10.7	51.1	10.3	51.9	11.7	45.9	9.2	3.30	0.02
Paranoid	57.3	5.7	51.8	10.1	55.3	9.9	46.6	9.5	4.29	0.007
Psychoticism	59.8	7.7	52.3	10.8	58.9	13.6	44.6	10.9	7.68	0.0009 <sup>c</sup>
Global severity index	57.8	9.0	52.7	10.6	56.9	12.5	44.3	10.1	8.00	0.0009 <sup>c</sup>

<sup>a</sup>For all patients,  $df=3, 121$ ; for patients reporting early abuse,  $df=3, 106$ .

<sup>b</sup>Both types of abuse,  $N=7$ ; physical abuse,  $N=44$ ; sexual abuse,  $N=9$ ; no abuse,  $N=65$ .

<sup>c</sup>Significant after Bonferroni correction for multiple comparisons.

<sup>d</sup>Both types of abuse,  $N=4$ ; physical abuse,  $N=34$ ; sexual abuse,  $N=7$ ; no abuse,  $N=65$ .

**TABLE 2. Numbers of Episodes of Physical and Sexual Abuse Reported by Male Psychiatric Outpatients**

Order of Perpetrators	N	Number of Abuse Episodes			
		Mean	SD	Median	Range
Physical abuse					
First perpetrator	34	9.9	11.8	4.5	1-45
Second perpetrator	16	3.8	3.2	3.0	1-10
Third perpetrator	9	3.1	2.9	1.0	1-10
Sexual abuse					
First perpetrator	10	3.4	5.6	1.0	1-20
Second perpetrator	1	1.0	—	1.0	—

of 6 years included three with both types of abuse, 14 with physical abuse only, and one with sexual abuse only. The sample size was too small to perform the one-way ANOVA for comparison.

The results of two-way ANOVAs with the two types of abuse as independent variables and the SCL-90-R scale scores as dependent variables were not significant, indicating that there was no interaction effect.

A probit regression analysis was carried out to determine if the global severity index of the SCL-90-R could correctly identify patients with histories of abuse. The scale correctly identified over 68% of the patients ( $\chi^2=20.4$ ,  $df=1$ ,  $p<0.0001$ ).

A stepwise multiple regression analysis was conducted with physical abuse and sexual abuse as the independent variables and the SCL-90-R global se-

verity index as the dependent variable. The results showed that physical abuse and sexual abuse were significant factors in predicting scores at the time of the first interview ( $F=10.7$ ,  $df=2, 122$ ,  $p<0.0002$ ). However, abuse accounted for only 15% of the variance, according to the coefficient of multiple determination, suggesting that other, unknown factors also were important.

#### *Number of Abuse Episodes*

Table 2 shows the mean, SD, median, and range of numbers of episodes of physical abuse and sexual abuse among the patients for whom the numbers of episodes were known. Of the 34 patients who reported being physically abused and gave the number of episodes of abuse by the first perpetrator, 16 were each abused by a second person and nine were abused by a third person. Of the 10 patients who each reported a history of sexual abuse and the number of episodes of abuse by the first perpetrator, one also reported abuse by a second perpetrator. The mean number of episodes of abuse by the first perpetrator was 9.9 for physical abuse and 3.4 for sexual abuse (table 2).

Pearson product-moment correlation coefficients were calculated for the relationship between total number of episodes of physical abuse and scores on each of the 10 scales of the SCL-90-R for the 34 pa-

tients who reported numbers of episodes. Only the correlation coefficient for the hostility scale was statistically significant ( $r=0.34$ ,  $df=32$ ,  $p<0.05$ ). The correlations between total number of episodes of sexual abuse and scores on each of the 10 scales of the SCL-90-R were not significant.

### *Psychiatric Diagnosis*

There were 59 different primary psychiatric diagnoses for the 125 patients. The rates of reported history of sexual abuse among the 35 patients with major affective illness, 32 with anxiety or dysthymic disorders, 20 with adjustment disorders, and 38 with all other diagnoses were 14%, 16%, 10%, and 11%, respectively. The rates of physical abuse were 51%, 41%, 25%, and 39%, respectively. The differences in these rates were not significant according to chi-square tests.

Of the 34 consecutive patients whose therapists were contacted, 16 reported abuse and 18 reported no abuse. A secondary axis II diagnosis of borderline personality disorder was found in four (25%) of the 16 abused patients and one (6%) of the 18 nonabused patients. The trend toward a higher rate of borderline personality disorder among those who were abused than among those who were not abused did not reach statistical significance, according to the chi-square test, in this subsample. However, the relative risk for borderline personality disorder among the patients who reported abuse compared to the others was 4.5. Of the 16 patients who reported abuse and whose therapists were contacted, eight (50%) were reported to have discussed the abuse in therapy.

### DISCUSSION

The results clearly show a high rate of reported history of physical abuse and a moderately high rate of reported sexual abuse among male psychiatric outpatients, as hypothesized. The total rate (48%) approaches the rates reported for female inpatients (72% [1] and 53% [13]) and for female outpatients (64% [our unpublished observations]). As is the case for female patients, many of the perpetrators of abuse were family members.

Furthermore, the patients who reported abuse had significantly higher SCL-90-R global severity indexes than those with no reported history of abuse; this finding confirms our second hypothesis. When the data were limited to only the patients reporting histories of abuse before the age of 18 years and those reporting abuse before age 12, the mean global severity index continued to be significantly higher for those with histories of abuse than for those who did not report abuse. These results are in line with the findings of Bryer et al. (1) for female inpatients. However, our results are nearly as dramatic even though one would expect that outpatients would be less seriously dis-

turbed than inpatients. There were nearly as many significant associations between history of abuse and SCL-90-R scores in the current study as in the Bryer et al. study (six versus eight). This suggests that abuse is associated with severity of symptoms in male outpatients. Since only 13 of the 45 patients who reported early abuse also experienced abuse at age 18 or later, there appears to be a persistent association between early abuse and high levels of symptoms, as measured by the SCL-90-R.

The mean numbers of episodes of reported physical abuse and reported sexual abuse by the first perpetrators were 9.9 and 3.4, respectively, suggesting that the abuse was not a casual occurrence. When we examined the correlations between number of episodes of physical or sexual abuse and scores on each of the 10 scales of the SCL-90-R, only the relationship between number of physical abuse episodes and the hostility scale score was statistically significant. The data suggest that the occurrence of physical abuse or sexual abuse, but not the number of episodes, is related to scores on the SCL-90-R scales, except for hostility. However, a much larger sample would be needed to thoroughly evaluate the relationship between episodes of abuse and scores on the scales of the SCL-90-R.

The overall rate of 13% for sexual abuse in the current study is higher than the 6% found in a survey of men in the Boston metropolitan area done by Finkelhor (14). In a study by Bell and Weinberg (15), 2.5% of male adults had had prepubertal sexual experiences with adult men. Although it is difficult to compare data from different surveys, because of the differences in the samples studied and in the methods of collecting data, there appears to be a higher rate of sexual abuse among male outpatients than among the general population. Although the clinic where we conducted our survey did not have a special service for abused patients, it makes sense that men who were more upset than the general population would have gravitated to a psychiatric clinic.

The 41% rate of physical abuse for the men in the current study is higher than the 13% reported for women in the general population by Mullen et al. (16). It is slightly lower than the 51% prevalence found for both adult female outpatients (our unpublished data) and inpatients (1). The lower rate of physical abuse for men is most likely due to either underreporting by men or the ability of older boys and men to ward off potential attackers.

Although using a questionnaire to obtain data has obvious limitations, a questionnaire can be a useful screening instrument for large populations, such as those in outpatient clinics. The relevance of the data is exemplified by the fact that 50% of the patients reporting abuse whose therapists were contacted discussed the abuse at some point in their therapy.

The finding of a relationship between the severity of adult psychiatric symptoms and a history of abuse corroborates other reports (1, 3, 13). The data suggest that abuse has persistent long-term effects on patients.

Current psychiatric symptoms were more severe among patients reporting histories of sexual abuse only or both physical and sexual abuse. The clinician generally should ask the patient about a history of each type of abuse. Furthermore, if one type of abuse is reported, it is worthwhile to ask about the other type as well. This may be particularly important when physical abuse has been reported because male patients may have more difficulty in discussing sexual abuse.

The higher rate of diagnosis of borderline personality disorder among abused patients whose therapists were contacted is similar to the findings of others (1, 17, 18). However, in future studies completion of a standard inventory of personality disorders (19) for each patient would be useful.

It may be worthwhile to consider diagnosing patients with histories of abuse as having posttraumatic stress disorder (PTSD) rather than other diagnoses (1, 20, 21). The perceived threat to one's physical integrity and the duration and intensity of disturbing thoughts and feelings would need to be carefully evaluated in order to make a diagnosis of PTSD.

Further information about the details of the abuse would be useful. However, a questionnaire was not appropriate for obtaining such information from new outpatients. Gentle elicitation of such information during clinical interviews in the context of psychotherapy would be a better approach.

Patients with histories of abuse, particularly early abuse, had higher levels of symptoms. It is important to explore with the patient the association between current symptoms and history of abuse, especially since the profile for disguised presentation (4) of the effects of abuse has not been described for men seeking help at an outpatient clinic. Particular reference to the patient's relationship to the perpetrator also is in order (22, 23). Denial and distortion may occur and need to be discussed in the process of working through the effects of the abuse. Finally, it may be difficult for many men to discuss abuse because the abuse might be more dystonic with sex role expectations for men.

In recent studies (24), 15% to 38% of adult women were found to have been sexually abused as children, and many of them also had experienced physical abuse. The patients with histories of early abuse had high rates of symptoms, such as anxiety and depression (16, 24). Men with histories of abuse might also be likely to gravitate to a psychiatric outpatient clinic for treatment of their psychopathology.

## REFERENCES

1. Bryer JB, Nelson BA, Miller JB, et al: Childhood sexual and physical abuse as factors in adult psychiatric illness. *Am J Psychiatry* 1987; 144:1426-1430
2. Herman J: Recognition and treatment of incestuous families. *Int J Family Therapy* 1983; 5:81-91
3. Carmen E(H), Rieker PP, Mills T: Victims of violence and psychiatric illness. *Am J Psychiatry* 1984; 141:378-383
4. Gelinas D: The persisting negative effects of incest. *Psychiatry* 1983; 46:312-332
5. Spencer M, Dunklee P: Sexual abuse of boys. *Pediatrics* 1986; 78:133-138
6. Pierce R, Pierce L: The sexually abused child: a comparison of male and female victims. *Child Abuse Negl* 1985; 9:191-199
7. Landis J: Experiences of 500 children with adult sexual deviation. *Psychiatr Q (Suppl)* 1955; 30:91-109
8. Creighton S: An epidemiological study of abused children and their families in the United Kingdom between 1977 and 1982. *Child Abuse Negl* 1985; 9:441-448
9. Baker A, Duncan S: Child sexual abuse: a study of prevalence in Great Britain. *Child Abuse Negl* 1985; 9:457-467
10. Derogatis LR: SCL-90-R Administration, Scoring, and Procedures Manual, II. Towson, Md, Clinical Psychometric Research, 1983
11. Belsley D, Kuh E, Welsch R: Regression Diagnostics: Identifying Influential Data and Sources of Collinearity. New York, John Wiley & Sons, 1980
12. Gunderson M: Retention of trainees—a study with dichotomous dependent variables. *J Econometrics* 1974; 2:79-93
13. Mills T, Rieker P, Carmen E: Hospitalization experiences of victims of abuse. *Victimology* 1984; 9:436-459
14. Finkelhor D: *Child Sexual Abuse—New Theory and Research*. New York, Free Press, 1984
15. Bell A, Weinberg M: *Homosexualities—A Study of Diversity Among Men and Women*. New York, Simon & Schuster, 1978
16. Mullen PE, Romans-Clarkson SE, Walton VA, et al: Impact of sexual and physical abuse on women's mental health. *Lancet* 1988; 1:841-845
17. Brooks B: Familial influences in father-daughter incest. *J Psychiatr Treatment and Evaluation* 1982; 4:117-124
18. Herman J: Histories of violence in an outpatient population: an exploratory study. *Am J Orthopsychiatry* 1986; 56:137-141
19. Millon T: *Millon Clinical Multiaxial Inventory*, 3rd ed. Minneapolis, Interpretive Scoring Systems, 1983
20. van der Kolk B, Greenberg M, Boyd H, et al: Inescapable shock, neurotransmitters, and addiction to trauma: toward a psychobiology of post traumatic stress. *Biol Psychiatry* 1985; 20:314-325
21. van der Kolk B: The psychological consequences of overwhelming life experiences, in *Psychological Trauma*. Edited by van der Kolk B. Washington, DC, American Psychiatric Press, 1986
22. Herman J: *Father-Daughter Incest*. Cambridge, Mass, Harvard University Press, 1981
23. Finkelhor D, Yllo K: *License to Rape—Sexual Abuse of Wives*. New York, Free Press, 1985
24. Bachmann G, Moeller T, Benett J: Childhood sexual abuse and the consequences in adult women. *Obstet Gynecol* 1988; 71: 631-642

# Major Depression in Patients With Social Phobia

Murray B. Stein, M.D., F.R.C.P.(C), Manuel E. Tancer, M.D.,  
Cheryl S. Gelernter, Ph.D., Bernard J. Vittone, M.D., and Thomas W. Uhde, M.D.

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*The authors examined the longitudinal course of affective illness retrospectively in 63 patients with social phobia and 54 patients with panic disorder. Significantly fewer (35%) of the patients with social phobia than patients with panic disorder (63%) had experienced at least one major depressive episode. Patients with generalized social phobia and patients with specific social phobia had comparable past rates of major depression (37% and 30%, respectively). The clinical and theoretical implications of these findings are discussed within the context of current concepts regarding the development of depressive symptoms in patients with anxiety disorders.*

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It has been recognized for many years that depression frequently occurs in patients with panic-agoraphobia syndromes. Sir Martin Roth, in an early description of the "phobic anxiety-depersonalization syndrome" (1), recognized that more than half of such patients experienced variable degrees of depression. Studies that have subsequently examined the occurrence of major depression in patients with panic disorder have found rates of between 25% and 70% (1-14), depending on the patient group examined (e.g., those with primary or secondary depression [8-13] versus those with secondary depression only [3-7, 14]).

In contrast, the literature is essentially devoid of studies examining the lifetime relationship between major depression and social phobia. Social phobia has been referred to as a "neglected anxiety disorder" (15), and this certainly applies to the study of affective illness in patients with social phobia. Since several studies have indicated that there may be considerable overlap between panic disorder and social phobia (16-18), we systematically examined the relative rates and

courses of affective illness in clinical samples of 63 patients with social phobia and 54 patients with panic disorder who were treated in an anxiety disorders clinic.

## METHOD

The data presented in this report derive from consecutively evaluated individuals participating in diagnostic interviews in our anxiety clinic between September 1987 and August 1988 who met *DSM-III-R* criteria for either social phobia or panic disorder. Patients were referred from physicians and other mental health professionals in the Washington, D.C., metropolitan area or were self-referred in response to advertisements in local newspapers.

Subjects who appeared likely to have social phobia (on the basis of information already obtained by telephone screening) were interviewed with the Anxiety Disorders Interview Schedule, Revised Version (19) and were also screened with a modified version of the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) (20), both of which were administered by the same experienced interviewer (C.S.G.). Patients with panic disorder were interviewed by an experienced research psychiatrist (M.B.S.) using a modified version of the Schedule for Affective Disorders and Schizophrenia—Lifetime Version for Anxiety Disorders (SADS-LA) (21). *DSM-III-R* diagnoses were applied; in cases where the diagnosis was unclear or in dispute, a consensual diagnosis was arrived at by group review of the interview material or, when necessary, reinterview of the subject by another investigator. As implied by *DSM-III-R*, panic disorder assumed a primary position in diagnostic classification; i.e., if social fear and avoidance came after the onset of "spontaneous" panic attacks, then a primary diagnosis of panic disorder was applied. Furthermore, in order to ensure homogeneity of the study populations and to militate against biased recall due to the presence of prevailing depression, subjects who currently met criteria for major depression (N=7) were excluded from the study. However, subjects who currently met criteria for dysthymic disorder (N=18: nine with panic disorder and nine with social phobia) were not excluded.

As part of the diagnostic interview process, the past

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occurrence and timing of lifetime episodes of major depression were documented by using *DSM-III-R* criteria. For purposes of this study, two research psychiatrists not only reviewed the mood disorder diagnoses that were made at the time of interview but also independently reviewed the compiled information about depressive episodes for each subject to assure that criteria were appropriately applied. When disagreements existed, consensual diagnoses were arrived at and used for this study.

Each subject's degree of functional impairment was rated by the interviewer following the diagnostic interview. The scale used for this purpose is a global clinical impression scale that asks the interviewer to rate functional impairment judged to be due to the psychiatric disorder on a 5-point scale (1=no symptoms and normal activity, 2=some symptoms are present, but they are not interfering with normal work or social activities, 3=symptoms are interfering with normal work or social activities in minor ways, 4=normal work or social activities interfered with markedly but not prevented or radically changed, and 5=normal work or social activities either radically changed or prevented) (22).

Age at onset was determined as the age at which full diagnostic criteria were met. For patients with social phobia, the onset of this disorder was frequently recalled as being "since early childhood" or "ever since I can remember." When onset was determined to be earlier than age 13, this was arbitrarily recorded as age 12 for statistical purposes.

Chi-square tests and Fisher's exact tests were used to compare categorical data. Continuous data were compared by using Student's *t* tests or Mann-Whitney *U* tests, where appropriate. All tests were two-tailed. All *p* values of 0.10 or more are reported as *n.s.*; *p* values of less than 0.10 are specifically reported. All data are expressed as means plus or minus standard deviations.

## RESULTS

Demographic characteristics of the subjects in the study are shown in table 1. There were no significant differences between the groups in gender, marital status, or current age.

Twenty-two (35%) of the 63 patients with social phobia had lifetime histories of at least one major depressive episode compared with 34 (63%) of 54 patients with panic disorder ( $\chi^2=9.16$ , *df*=1, *p*<0.005).

The subjects with social phobia were subdivided into those with generalized (*N*=43) or specific (*N*=20) social phobia. We considered the social phobia to be specific if it was limited to one or two discrete situations (e.g., public speaking or writing in front of others). We considered it generalized if the patient's syndrome included more global avoidance of social (particularly interpersonal) contact. It was hypothesized that patients with social phobia with generalized social anxiety and avoidance would be more prone to

**TABLE 1. Characteristics of Clinical Samples of Patients With Social Phobia or Panic Disorder**

Characteristic	Patients With Social Phobia (N=63)	Patients With Panic Disorder (N=54)
Gender		
Men		
Number	24	21
Percent	38	39
Women		
Number	39	33
Percent	62	61
Marital status		
Married		
Number	35	38
Percent	56	70
Never married		
Number	28	16
Percent	44	30
Current age (years)		
Mean	36.5	36.4
SD	9.6	8.4
Age at onset (years) <sup>a</sup>		
Mean	15.2	27.5
SD	3.7	10.2
Duration of illness (years) <sup>b</sup>		
Mean	21.0	8.9
SD	9.7	8.1
Degree of global functional impairment <sup>c</sup>		
2-3		
Number	6	19
Percent	10	35
4-5		
Number	57	35
Percent	90	65

<sup>a</sup>The patients with social phobia had a significantly earlier age at onset (Mann-Whitney *U*=326.00, *p*<0.00005).

<sup>b</sup>The patients with social phobia had been ill significantly longer (*t*=7.27, *df*=114, *p*<0.0001).

<sup>c</sup>1=no symptoms and normal activity; 5=radical changes in work or social activities. The patients with social phobia were significantly more impaired (continuity-adjusted  $\chi^2=9.92$ , *df*=1, *p*<0.002).

depression than those with specific social fears. However, these two subgroups did not differ in their lifetime rates of major depression: 16 (37%) of the 43 patients with generalized social phobia had experienced at least one previous major depression, compared with six (30%) of the 20 patients with specific social phobia ( $\chi^2=0.31$ , *df*=1, *n.s.*). Similarly, when the patients with panic disorder were subdivided into those with (*N*=38) and without (*N*=16) agoraphobia, the two groups were found to have comparable rates of major depressive episode (68% [*N*=26] versus 50% [*N*=8], respectively;  $\chi^2=1.64$ , *df*=1, *n.s.*).

The temporal relationship between the onset of social phobia and the first major depressive episode was examined in the subjects with social phobia who had a history of major depression (*N*=22). If this interval was 2 months or less, they were considered to have been concurrent in onset. One (5%) of the 22 subjects with social phobia and a history of major depression had his first major depressive episode 11 years before the onset of social phobia, and one (5%) had his first

major depressive episode concurrent with the onset of social phobia, but 20 (91%) had their first major depressive episode  $13.2 \pm 7.9$  years after the onset of social phobia (range=1–26 years).

## DISCUSSION

We found that social phobia is associated with a substantially lower rate of depression than is panic disorder (35% versus 63%, respectively). We can infer from these preliminary data that not all anxiety disorders are alike in their rates of major depression. Although there are several methodologic limitations to our study (e.g., the sample was clinical rather than epidemiologic and the study was retrospective rather than prospective), our findings raise a number of interesting points.

For example, not all anxiety disorders would appear to be associated with the same degree of functional impairment. The patients with social phobia were more severely impaired in terms of day-to-day functioning (see table 1), but they were less prone to the development of major depression. This would seem to contradict the idea that patients with anxiety disorders develop depression as a direct consequence of the demoralization they experience as a result of living with chronic anxiety and phobic limitations. Nonetheless, one possible explanation for our findings is that social phobia (even when generalized) occurs in response to relatively discrete, predictable, and avoidable situations. This contrasts with panic disorder in that panic attacks seem to be spontaneous and therefore less controllable. It has been recognized that when faced with the same amount of stress under controllable or uncontrollable conditions, individuals experience the greatest dysphoria and neuroendocrine hyperactivity when the stress is uncontrollable (23). The uncontrollable nature of panic attacks may engender greater feelings of helplessness and thus contribute to a greater propensity for depression.

The goals of future research will be to broaden and refine our understanding of the psychological, neuroendocrine, and genetic factors that might contribute to higher rates of major depression in patients with panic disorder (1–14, 24) than in patients with social phobia.

## REFERENCES

1. Roth M: The phobic anxiety-depersonalization syndrome. *Proc R Soc Med* 1959; 52:587–595
2. Roth M, Gurney C, Garside RF, et al: Studies in the classification of affective disorders: the relationship between anxiety states and depressive illness, I. *Br J Psychiatry* 1972; 121:146–161
3. Woodruff RA, Guze SB, Clayton PJ: Anxiety neurosis among psychiatric outpatients. *Compr Psychiatry* 1972; 13:165–170
4. Schapira K, Roth M, Kerr TA, et al: The prognosis of affective disorders: the differentiation of anxiety states from depressive illnesses. *Br J Psychiatry* 1972; 121:175–181
5. Clancy J, Noyes R, Hoehn PR, et al: Secondary depression in anxiety neurosis. *J Nerv Ment Dis* 1978; 166:846–850
6. Cloninger CR, Martin RL, Clayton P, et al: A blind follow-up and family study of anxiety neurosis: preliminary analysis of the St Louis 500, in *Anxiety: New Research and Changing Concepts*. Edited by Klein DI, Rabkin J. New York, Raven Press, 1981
7. Dealy RS, Ishiki DM, Avery DH, et al: Secondary depression in anxiety disorders. *Compr Psychiatry* 1981; 22:612–618
8. Munjack DJ, Moss HB: Affective disorder and alcoholism in families of agoraphobics. *Arch Gen Psychiatry* 1981; 38:869–871
9. Raskin M, Peeke HVS, Dickman W, et al: Panic and generalized anxiety disorders: developmental antecedents and precipitants. *Arch Gen Psychiatry* 1982; 39:687–689
10. Breier A, Charney DS, Heninger GR: Major depression in patients with agoraphobia and panic disorder. *Arch Gen Psychiatry* 1984; 41:1125–1135
11. Breier A, Charney DS, Heninger GR: The diagnostic validity of anxiety disorders and their relationship to depressive illness. *Am J Psychiatry* 1985; 142:787–797
12. Uhde TW, Boulenger J-P, Roy-Byrne PP, et al: Longitudinal course of panic disorder: clinical and biological considerations. *Prog Neuropsychopharmacol Biol Psychiatry* 1985; 9:39–51
13. Buller R, Maier W, Benkert O: Clinical subtypes in panic disorder: their descriptive and prospective validity. *J Affective Disord* 1986; 11:105–114
14. Lesser IM, Rubin RT, Pecknold JC, et al: Secondary depression in panic disorder and agoraphobia, I: frequency, severity, and response to treatment. *Arch Gen Psychiatry* 1988; 45:437–443
15. Liebowitz MR, Gorman JM, Fyer AJ, et al: Social phobia: review of a neglected anxiety disorder. *Arch Gen Psychiatry* 1985; 42:729–736
16. Barlow DH, DiNardo PA, Vermilyea BB, et al: Co-morbidity and depression among the anxiety disorders. *J Nerv Ment Dis* 1986; 174:63–71
17. Goldstein S: Three cases of overlap between panic disorder, social phobia, and agoraphobia. *J Clin Psychiatry* 1987; 48:452–453
18. Stein MB, Shea CA, Uhde TW: Social phobic symptoms in patients with panic disorder: clinical and theoretical implications. *Am J Psychiatry* 1989; 146:235–238
19. DiNardo PA, O'Brien GT, Barlow DH, et al: Reliability of DSM-III anxiety disorder categories using a new structured interview. *Arch Gen Psychiatry* 1983; 40:1070–1074
20. Endicott J, Spitzer RL: A diagnostic interview: the Schedule for Affective Disorders and Schizophrenia. *Arch Gen Psychiatry* 1978; 35:837–844
21. Fyer AJ, Endicott J, Mannuzza S, et al: Schedule for Affective Disorders and Schizophrenia—Lifetime Version, Modified for the Study of Anxiety Disorders. New York, New York State Psychiatric Institute, Anxiety Disorders Clinic, March 1985
22. Cooper JE: A study of behaviour therapy in 30 psychiatric patients. *Lancet* 1963; 1:411–415
23. Breier A, Albus M, Pickar D, et al: Controllable and uncontrollable stress in humans: alterations in mood and neuroendocrine and psychophysiological function. *Am J Psychiatry* 1987; 144:1419–1425
24. Stein MB, Uhde TW: Panic disorder and major depression: a tale of two syndromes. *Psychiatr Clin North Am* 1988; 11:441–461

# Impact of Life Events on Subjects With Panic Disorder and on Comparison Subjects

Ronald M. Rapee, Ph.D., Eric M. Litwin, B.A., and David H. Barlow, Ph.D.

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*A questionnaire measure of major life events was given to 64 subjects with diagnoses of panic disorder with agoraphobia, 33 subjects with other anxiety disorders, and 34 nonanxious subjects. Anxious subjects indicated the life events that had occurred in the 6-month period immediately before their current disorder began and rated the impact of each event on a 7-point scale. Nonanxious subjects made the same ratings for a 6-month period 1½–2 years before the study. There was no significant difference between groups in the number of life events reported. However, anxious subjects rated these events as having a significantly greater negative impact than did nonanxious subjects.*

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A number of authors have suggested that stress plays a major role in the etiology of panic disorder (1–3). This suggestion has been based on a large number of surveys which have found that stressful events are present in the lives of a majority of patients with panic disorder before the onset of their first panic attacks (1). In general, these surveys indicate that approximately 80% of individuals with panic disorder report that a major stressor occurred before the onset of the disorder, although the patients themselves seldom make any connection between the stressor and the first panic attack (1).

Unfortunately, few of these studies have included appropriate comparison groups. Two studies that compared life events of panic disorder subjects and nonanxious subjects had equivocal results. Whereas one study (4) found a significant difference in the numbers of life events reported by panic disorder patients and by nonanxious subjects, another study (5) did not find a difference between these groups in the total number of events but, rather, in the number of events that happened to the individuals personally.

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Received April 25, 1989; revision received Oct. 11, 1989; accepted Nov. 8, 1989. From the Center for Stress and Anxiety Disorders, State University of New York at Albany, and the Department of Psychology, University of Queensland. Address reprint requests to Dr. Rapee, Department of Psychology, University of Queensland, St. Lucia, Queensland 4067, Australia.

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It could be argued, however, that nonanxious subjects are not an appropriate comparison group. To demonstrate the importance of life events specifically in patients with panic disorder, it is necessary to have studies that compare panic disorder subjects and subjects with other anxiety disorders. The only studies that have done this to date have had either a very small sample size (6) or unclear diagnostic criteria by current standards (7). Thus, we felt that it was important to conduct a study which compared the life events reported by subjects with panic disorder, subjects with other DSM-III-R anxiety disorders, and nonanxious subjects.

## METHOD

### Subjects

The subjects for the study were 154 persons meeting the DSM-III-R criteria for an anxiety disorder and 36 nonanxious persons. Anxiety disorder subjects were given diagnoses with the use of a structured clinical interview, the Anxiety Disorders Interview Schedule—Revised, an earlier version of which has been shown to yield reliable diagnostic judgments (8). As part of the interview, the subject's age at the onset of the current disorder (to the best of his or her recollection) was carefully determined. This age was then compared with the age the subject reported on the modified Life Experiences Survey (9) to ensure that he or she was referring to the same disorder. If the ages were not within 6 months of each other, the data for that subject were excluded from the analysis.

A total of 57 anxiety disorder subjects were excluded from the study for the following reasons: not reporting age at onset on the questionnaire (12 subjects), not being able to specify age at onset during the interview (22 subjects; 18 of these were persons without panic disorder), or age at onset reported on the questionnaire was not within 6 months of age at onset reported during the interview (23 subjects). This left a total of 97 anxiety disorder subjects: 64 with panic disorder and various degrees of agoraphobic avoidance and 33 with other DSM-III-R anxiety disorders.

The mean  $\pm$  SD age of the panic disorder group was  $32.0 \pm 6.9$  years; 39 (61%) were female. The median

duration of the disorder was 21.5 months. The mean age of the group with other anxiety disorders was  $34.6 \pm 9.3$  years; 20 (61%) were female. The median duration of their disorders was 48.0 months.

The nonanxious subjects were volunteers who reported never having had a diagnosis of or having sought treatment for a psychological disorder. They were recruited both through patients at our clinic and through advertisements placed in local community centers. Those recruited through clinic patients were friends and acquaintances, but not relatives, of the patients. All of the nonanxious subjects were paid for their participation. Thirty-six subjects were originally recruited, but two were excluded (one did not complete the questionnaire properly, and the other reported just beginning treatment for an anxiety disorder), leaving a total of 34 nonanxious subjects. This group had a mean age of  $34.7 \pm 10.3$  years; it included 16 women (47%).

### Measure

All subjects were asked to complete a modified version of the Life Experiences Survey (9), a 76-item self-report survey of positive and negative life experiences that have occurred in the past year. Respondents are instructed to endorse all items that apply and to rate, on a 7-point scale (from  $-3$ =extremely negative to  $3$ =extremely positive), the perceived impact of each event on their lives. The questionnaire appears to have reasonable psychometric properties (9). For the present study it was modified slightly by asking respondents to endorse those events which occurred in the 6-month period immediately before the onset of the current problem or disorder. Before answering the questionnaire, the respondents were instructed to think of a number of aspects of their lives at the time (their age, relationships, work, etc.) to help pinpoint the time frame in their minds. Two life events were added to the original survey: "direct exposure to traumatic (life threatening) event" and "bad experience with mood-altering drug or alcohol." This resulted in a total of 78 possible life events on the revised Life Experiences Survey. In addition, three spaces were left at the end for listing individual events that were not included in the questionnaire.

Nonanxious subjects were given a form of the questionnaire which included the same instructions except that they were asked to endorse items which had occurred during a 6-month period  $1\frac{1}{2}$ –2 years before the study. This period was chosen to provide a retrospective view which would be roughly equivalent to that of the panic disorder group.

To examine some specific potential differences in the data, the life events listed in the modified Life Experiences Survey were subdivided into mutually exclusive groups in two different ways. In the first subdivision, the events were divided into groups of positive events (e.g., outstanding personal achievement, marital reconciliation;  $N=5$ ), negative events (e.g., trouble with

employer, miscarriage;  $N=35$ ), and ambiguous events (e.g., pregnancy, new job;  $N=38$ ). In the second subdivision, the events were divided into groups of health-related events (e.g., abortion, major personal illness or injury;  $N=28$ ), relationship-related events not concerned with health (e.g., marriage, trouble with in-laws;  $N=14$ ), career/finance-related events (e.g., changed work situation, being fired from job;  $N=17$ ), and miscellaneous events (e.g., detention in jail, outstanding personal achievement;  $N=19$ ). These divisions were selected because we felt that they were relevant to suggestions in the literature and certain theories about panic disorder.

In each analysis, the findings for the main question (total questionnaire result) were examined for statistical significance with alpha set at 0.05. Since our seven questions were essentially exploratory ones being investigated with the same data, we thought that it was important to control for possible inflation of the type I error rate by using a modified Bonferroni correction (10). This yielded a critical alpha of 0.014 for these questions.

### RESULTS

The numbers of subjects in each diagnostic category who reported experiencing at least one life event on the revised Life Experiences Survey were compared by means of a chi-square analysis. The results are reported in table 1. There was an overall significant difference in the number of subjects in each group who reported at least one life event in the 6-month period specified. Follow-up chi-square tests were used to examine the source of the difference on this variable. The only significant difference was between the panic disorder group and the other anxiety disorders group ( $\chi^2=7.19$ ,  $df=1$ ,  $p<0.05$ ). There was no significant difference between the panic disorder group and the nonanxious comparison group ( $\chi^2=2.93$ ,  $df=1$ , n.s.).

As can be seen in table 1, there were no significant differences between groups on the various subdivisions of stressors. Since the subdivision of life events had been somewhat arbitrary, a series of chi-square tests were conducted on the number of subjects in each group who reported each one of the 78 life events. Even without a correction for the type I error rate, there were no significant differences between groups in the numbers of subjects reporting any individual life event.

Table 2 lists the mean numbers of life events reported by the subjects in each of the three groups, including subjects who reported no events in the period. According to one-way analyses of variance (ANOVAs), there were no significant differences between the diagnostic groups in total number of events recorded or any of the subgroupings of events.

The impact of each type of life event (rated on the 7-point scale from  $-3$  to  $3$ ) for the three groups was compared by using one-way ANOVAs. There was a



**TABLE 1. Subjects With Panic Disorder or Other Anxiety Disorders and Nonanxious Subjects Who Reported at Least One Major Life Event in a 6-Month Period**

Event Category	Subjects With Panic Disorder (N=64)		Subjects With Other Anxiety Disorders (N=33)		Nonanxious Subjects (N=34)		$\chi^2$ (df=2)
	N	%	N	%	N	%	
Total	63	98.4	28	84.8	31	91.2	6.56 <sup>a</sup>
First grouping							
Negative	44	68.8	16	48.5	17	50.0	5.15
Positive	21	32.8	13	39.4	20	58.8	6.26
Ambiguous	62	96.9	26	78.8	29	85.3	8.24
Second grouping							
Health	39	60.9	14	42.4	14	41.2	4.81
Relationship	47	73.4	22	66.7	24	70.6	0.49
Career/finance	50	78.1	21	63.6	28	82.4	3.62
Miscellaneous	58	90.6	23	69.7	27	79.4	6.88

<sup>a</sup>p<0.05.**TABLE 2. Number of Major Life Events in a 6-Month Period Reported by Subjects With Panic Disorder or Other Anxiety Disorders and by Nonanxious Subjects**

Event Category	Number of Events						F (df=2, 128)
	Subjects With Panic Disorder (N=64)		Subjects With Other Anxiety Disorders (N=33)		Nonanxious Subjects (N=34)		
	Mean	SD	Mean	SD	Mean	SD	
Total	9.0	5.2	7.8	7.0	7.9	5.8	0.66
First grouping							
Negative	1.7	1.8	1.3	2.1	1.2	1.6	1.02
Positive	0.4	0.7	0.5	0.6	0.6	0.6	1.30
Ambiguous	6.1	3.6	5.6	5.2	5.6	4.1	0.18
Second grouping							
Health	1.2	1.3	1.2	2.2	0.8	1.2	0.86
Relationship	1.3	1.2	1.6	2.0	1.4	1.2	0.56
Career/finance	2.0	1.9	1.4	1.6	1.8	1.3	1.23
Miscellaneous	3.3	2.3	2.8	2.7	3.0	2.6	0.40

highly significant difference in the mean impact of stressors across the three diagnostic groups (see table 3). Following these ANOVAs, Duncan's multiple range tests revealed that the ratings for the panic disorder group (−0.9) and the other anxiety disorders group (−0.9) did not differ significantly, but they were significantly different from the rating for the nonanxious group (0.5). As can be seen in table 3, similar differences were found in the impact of negative events, ambiguous events, career/finance events, and miscellaneous events. There was an overall significant difference in relationship events, but in this category the other anxiety disorders group scored significantly lower (−1.3) than both the panic disorder group (0.0) and the nonanxious group (0.5), which did not differ significantly from each other.

## DISCUSSION

Overall, this study resulted in two broad findings. First, the panic disorder subjects did not report signifi-

cantly more major life events before the onset of their disorder than did the subjects with other anxiety disorders or the nonanxious subjects during an equivalent period. Second, the anxious subjects—those with panic disorder and those with other anxiety disorders—reported that life events experienced before the onset of the disorder had a more negative impact than those reported by the nonanxious subjects.

The findings related to the proportion of subjects in each group who reported at least one life event were equivocal. While the overall difference was statistically significant, more specific analysis indicated that the panic disorder subjects were more likely to report a life event than the other anxiety disorders group but were not more likely to report such an event than the nonanxious subjects. In addition, there were no significant differences in the numbers of subjects reporting any individual life event. Thus, the overall significant difference in number of life events between subjects with panic disorder and subjects with other anxiety disorders may well have been an accidental statistical effect.

**TABLE 3. Impact of Major Life Events in a 6-Month Period Reported by Subjects With Panic Disorder or Other Anxiety Disorders and by Nonanxious Subjects**

Event Category	Rating of Impact of Events <sup>a</sup>						F	df
	Subjects With Panic Disorder (N=64)		Subjects With Other Anxiety Disorders (N=33)		Nonanxious Subjects (N=34)			
	Mean	SD	Mean	SD	Mean	SD		
Total	-0.9 <sub>a</sub>	1.2	-0.9 <sub>a</sub>	1.3	0.5 <sub>b</sub>	1.3	16.70 <sup>b</sup>	2, 119
First grouping								
Negative	-2.0 <sub>a</sub>	1.2	-1.8 <sub>a</sub>	0.9	-1.0 <sub>b</sub>	1.1	5.52 <sup>c</sup>	2, 74
Positive	1.7	1.5	0.7	2.3	2.3	0.8	4.23	2, 51
Ambiguous	-0.7 <sub>a</sub>	1.3	-0.9 <sub>a</sub>	1.4	0.6 <sub>b</sub>	1.2	11.83 <sup>b</sup>	2, 114
Second grouping								
Health	-2.0	1.2	-1.6	1.1	-1.1	1.1	3.01	2, 64
Relationship	0.0 <sub>a</sub>	2.0	-1.3 <sub>b</sub>	1.5	0.5 <sub>a</sub>	1.8	5.62 <sup>c</sup>	2, 90
Career/finance	-0.5 <sub>a</sub>	1.8	-1.0 <sub>a</sub>	1.6	0.4 <sub>b</sub>	1.7	4.90 <sup>c</sup>	2, 96
Miscellaneous	-0.8 <sub>a</sub>	1.3	-0.6 <sub>a</sub>	1.6	0.8 <sub>b</sub>	1.3	12.56 <sup>b</sup>	2, 105

<sup>a</sup>Seven-point scale (-3=extremely negative, 3=extremely positive). Means sharing subscripts are not significantly different at the 0.05 level according to Duncan's multiple range test.

<sup>b</sup> $p < 0.001$ .

<sup>c</sup> $p < 0.01$ .

Data from this study, which used a questionnaire, are in agreement with interview data from a small sample (6) in which patients with panic disorder and those with generalized anxiety disorder reported no difference in stressors at onset. In addition, the data are somewhat consistent with results of a study by Roy-Byrne et al. (5) that found no significant difference between the total numbers of stressors reported at onset by panic disorder subjects and by a group of non-anxious control subjects. The results of the Roy-Byrne et al. study did indicate a difference between the two groups in the number of stressors that happened to the individual personally. To examine this possibility, we conducted a post hoc analysis on our data that included the items which appeared to apply only to life events that happened to the individual subjects themselves. There were no significant differences in number of stressors between the groups (panic disorder, mean  $\pm$  SD =  $6.9 \pm 4.4$ , anxiety disorder,  $6.1 \pm 5.4$ , nonanxious,  $6.4 \pm 4.5$ ;  $F = 4.3$ ,  $df = 2, 128$ , *n.s.*). The differences between the findings of Roy-Byrne et al. and our data may be due to the different methods used (questionnaire versus interview). Both methods have their advantages. Interview studies allow investigation of more detailed questions but are more open to experimenter bias. Prospective studies that use both methods may be necessary to examine questions completely.

It is interesting that while the numbers of stressors did not differ between groups, there was a major difference in the perceived impact of these life events. Both of the anxious groups reported a significantly more negative impact of the life events than did the nonanxious group. There are a number of possible explanations for this result.

It may be argued that anxious subjects do indeed experience more objectively negative events than nonanxious subjects. However, subdivision of the

events into negative and positive groups did not indicate significant differences between groups in the numbers of each type of stressor, and previous studies have found similar results (5).

A second argument suggests that because of their current mood state, anxious subjects recall the impact of life events as more negative than they actually seemed to be at the time (11). Since the frequency of reported positive and negative events did not differ between groups, the difference in impact is not likely to have been due to differential recall. Rather, any effects of current mood state were likely to have been on the reporting. In other words, anxious subjects may report the impact of earlier life events in a manner consistent with their current mood.

A third argument, similar to the second, is that anxious subjects see a causal connection between earlier life events and their present symptoms. They may then exaggerate the impact of these events in line with such a post hoc explanation.

A final possible explanation is that anxious subjects have premorbid characteristics which cause them to perceive life events as particularly negative. The corollary would be that life events per se are not a sufficient cause for anxiety disorders, but that they may act as triggers given particular preexisting personality features. A number of theories about anxiety disorders stress the importance of trait variables, such as a sense of lack of control, as vulnerability factors (1). In this view life events would be seen by the individual as more uncontrollable and hence more negative.

In summary, while earlier studies suggested that panic disorder is preceded by major life events in about 80% of those who suffer from the disorder (1), this study provided data to suggest that the number of such events may be no greater than that found for subjects with other anxiety disorders or for nonanxious sub-

jects. However, consistent with earlier findings (5, 12), the data suggest that anxious subjects tend to perceive the impact of the life stressors that they have experienced as more negative than do nonanxious subjects. There are a number of possible explanations for this result, and prospective studies will be needed to select from among them.

## REFERENCES

1. Barlow DH: Anxiety and Its Disorders: The Nature and Treatment of Anxiety and Panic. New York, Guilford Press, 1988
2. Margraf J, Ehlers A, Roth WT: Panic attacks: theoretical models and empirical evidence, in Panic and Phobias. Edited by Hand I, Wittchen HU. Berlin, Springer, 1986
3. Mathews AM, Gelder MG, Johnston DW: Agoraphobia: Nature and Treatment. New York, Guilford Press, 1981
4. Faravelli C: Life events preceding the onset of panic disorder. *J Affective Disord* 1985; 9:103–105
5. Roy-Byrne PP, Geraci M, Uhde TW: Life events and the onset of panic disorder. *Am J Psychiatry* 1986; 143:1424–1427
6. Hibbert GA: Ideational components of anxiety: their origin and content. *Br J Psychiatry* 1984; 144:618–624
7. Roth M: The phobic anxiety-depersonalisation syndrome. *Proc R Soc Med* 1959; 52:587–596
8. Di Nardo PA, O'Brien GT, Barlow DH, et al: Reliability of DSM-III anxiety disorder categories using a new structured interview. *Arch Gen Psychiatry* 1983; 40:1070–1074
9. Sarason IG, Johnson JH, Seigel JM: Assessing the impact of life experiences. *J Consult Clin Psychol* 1978; 46:932–946
10. Keppel G: Design and Analysis: A Researcher's Handbook. Englewood Cliffs, NJ, Prentice-Hall, 1982
11. Bower GH: Mood and memory. *Am Psychol* 1981; 36:129–148
12. Tennant C, Andrews G: The pathogenic quality of life stress in neurotic impairment. *Arch Gen Psychiatry* 1978; 35:859–863

# Convergent Validity of Measures of PTSD in Vietnam Combat Veterans

Miles E. McFall, Ph.D., Dale E. Smith, Ph.D., Douglas K. Roszell, M.D.,  
David J. Tarver, Ph.D., and Kenneth L. Malas, M.D.

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*The authors evaluated the convergent validity of several widely used psychometric tests of posttraumatic stress disorder (PTSD) symptoms against DSM-III-R criteria for PTSD in 130 Vietnam combat veterans. Significant positive correlations were found between these instruments and the number of DSM-III-R symptoms endorsed, supporting the validity of psychometric instruments as continuous measures of PTSD symptom severity. The various psychometric measures also correlated moderately with one another, suggesting that they assess related but somewhat separate PTSD phenomena. Finally, predicted relationships between stressors and symptoms were supported by significant correlations between degree of traumatic combat exposure and DSM-III-R and psychometric indexes of PTSD.*

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The recently completed National Vietnam Veterans Readjustment Study estimated that 479,000 Vietnam veterans suffer from posttraumatic stress disorder (PTSD) and that an additional 350,000 veterans have partial PTSD (1). Development of valid diagnostic instruments is essential for identifying these troubled veterans, for treatment planning, for quantification of symptom severity in research studies, and for decision making regarding disability compensation.

A number of psychometric tests have been developed to measure PTSD symptoms, including the Impact of Event Scale (2), the PTSD subscale of the MMPI (3), and the Mississippi Scale for Combat-Related PTSD (4). These measures are highly reliable and accurately discriminate combat veterans with PTSD

from various comparison groups (1). In a number of validation studies (1, 3-5), scores for these instruments have been identified that optimize the percentage of individuals correctly classified as having or not having PTSD (sensitivity and specificity). Validation studies conducted to date, however, have not provided information regarding the association between quantitative scores on these psychometric measures and the degree of severity of PTSD assessed by DSM-III-R criteria. It is important to establish that psychometric indexes are sensitive to gradations in PTSD symptoms, since psychiatric disorders may be usefully conceptualized in dimensional rather than purely categorical terms (6). Moreover, measures that validly assess PTSD on a continuum of severity may be useful in clinical situations, where quantification of the degree of symptom severity is necessary (e.g., subthreshold levels of the disorder where the requisite number of symptoms are not endorsed to establish the diagnosis), and in research studies, where interval scale measures of PTSD can serve as outcome variables and as covariates that predict responsiveness to experimental procedures.

One purpose of the present study is to provide convergent validation of widely used psychometric tests as continuous measures of PTSD symptoms identified by DSM-III-R criteria. We also investigated which of these psychometric indexes are most highly associated with or predictive of DSM-III-R PTSD symptoms. In addition, we examined the correlation of these psychometric instruments with one another in order to evaluate the extent to which they measure the same psychological phenomena. Finally, since degree of traumatic stress is presumed to be etiologically related to development and severity of PTSD (7), we evaluated the expected positive association between measures of PTSD and intensity of traumatic exposure.

## METHOD

### Subjects

The subjects were 130 Vietnam combat veterans referred to the Seattle VA Medical Center PTSD Clinical Team for diagnosis and intervention. Seventy-seven (59%) of the patients were referred from inpatient psy-

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Received June 1, 1989; revision received Oct. 25, 1989; accepted Nov. 8, 1989. From the Seattle VA Medical Center and the Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle. Address reprint requests to Dr. McFall, Seattle VA Medical Center, Psychology Service (116A), 1660 South Columbian Way, Seattle, WA 98108.

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chiatry units, and 53 (41%) were evaluated as outpatients. The subjects' mean $\pm$ SD age was 40.9 $\pm$ 3.2 years. The sample was largely Caucasian (110 subjects—84.6%), but black (N=10—7.7%), Native American (N=4—3.1%), Hispanic (N=3—2.3%), and Asian (N=3—2.3%) veterans were also represented. All subjects had a history of combat duty in the Army (N=88—67.7%), Marines (N=27—20.8%), Navy (N=9—6.9%), or Air Force (N=6—4.6%). Subjects' mean $\pm$ SD score was 9.4 $\pm$ 3.3 on the Revised Combat Scale, a 14-point scale on which a score of 10 or above indicates high combat exposure (8). One hundred fifteen (88.5%) of the subjects met full *DSM-III-R* criteria for PTSD, and the remaining 15 subjects (11.5%) had subthreshold levels of the disorder.

#### *Assessment Instruments and Procedure*

*Structured Clinical Interview for DSM-III-R (SCID-R)* (9). We used the SCID-R to make the *DSM-III-R* diagnosis of PTSD. This instrument provides operational criteria for assessing the 17 symptoms of PTSD within the criterion categories of reexperiencing, numbing-avoidance, and physiological arousal. The SCID-R was administered by Board-certified psychiatrists (D.K.R. and K.L.M.) and clinical psychologists (M.E.M. and D.E.S.) who had several years of experience in assessment and management of combat-related PTSD. Interrater agreement was assessed by having two clinicians (D.K.R. and D.E.S.) complete the SCID-R on a randomly selected subsample of 10 patients. Agreement on the decision to assign a diagnosis of PTSD was 100%. For each patient, the number of symptoms positively endorsed was summed to arrive at an index of PTSD symptom severity.

*Impact of Event Scale.* The Impact of Event Scale (2) is a 15-item scale measuring two core phenomena of PTSD: 1) ideational and affective reexperiencing of traumatic events and 2) defensive avoidance and/or denial of trauma-related memories and emotions. Zilberg et al. (10) reported the interscale correlation to be 0.42, indicating that these dimensions assess separate but related phenomena. Several studies have demonstrated excellent discriminant validity for the Impact of Event Scale in distinguishing patients with PTSD symptoms from traumatized asymptomatic control subjects in military and nonmilitary populations (1, 5, 10). Mean scores for Vietnam combat veterans have been reported to be 25.6 for the intrusion subscale and 27.7 for the avoidance subscale (1).

*PTSD subscale of the MMPI.* The PTSD subscale of the MMPI (3) consists of 49 items from the MMPI found to discriminate psychiatric patients with mixed diagnoses but no PTSD from Vietnam combat veterans with PTSD diagnosed by elaborate psychophysiological and interview procedures. A minimum subscale score of 30 has been used as the criterion indicating the presence of PTSD. Correct classification of PTSD and non-PTSD subjects has ranged from 66% to 82% in various studies (1, 3, 11, 12).

*Mississippi Scale for Combat-Related PTSD.* The Mississippi Scale for Combat-Related PTSD (4) is a 35-item Likert-scaled questionnaire originally developed to assess *DSM-III* PTSD symptoms and various associated features in Vietnam veterans who had been exposed to combat. The Mississippi scale has high internal consistency ( $\alpha=0.94$ ). A score above 106 has been shown to have high sensitivity (93%) and specificity (89%) in discriminating combat veteran patients with PTSD from noncombat Vietnam-era psychiatric patients and nonpatient Vietnam veterans (4). Subsequent validation studies of the Mississippi scale have found similarly high levels of sensitivity and specificity in discriminating patients with PTSD from various non-PTSD control subjects (1, 13).

*Vietnam Era Stress Inventory.* The Vietnam Era Stress Inventory (unpublished 1984 paper by J.P. Wilson and G.E. Krauss) was administered to assess exposure to specific stressors in the Vietnam conflict. Forty items of the 44-item inventory were administered that have been shown, through factor analysis, to define dimensions of injury or death and exposure to ecological stressors (13; unpublished 1984 paper by J.P. Wilson and G.E. Krauss). Reliability analysis has demonstrated high internal consistency for the total scale ( $\alpha=0.94$ ), and corrected correlations between items and the total score averaged 0.50 (13).

Patients were administered the SCID-R, the psychometric instruments, and the Vietnam Era Stress Inventory during the course of a 4–8-hour clinical assessment.

#### RESULTS

Table 1 presents the matrix of Pearson product-moment correlation coefficients among measures. Statistically significant positive correlations were obtained between the SCID-R and all psychometric indexes of PTSD. The strongest relationship was clearly with the Mississippi Scale for Combat-Related PTSD, which accounted for 42% of the variance in PTSD symptoms measured by the SCID-R. A stepwise multiple regression analysis was performed to predict SCID-R scores from psychometric measures of PTSD and combat exposure. In this analysis, only the Mississippi scale entered the equation, indicating that the other measures did not contribute to prediction of SCID-R scores beyond the Mississippi scale.

Correlations among psychometric measures of PTSD showed a moderately strong association between the Mississippi scale and the Impact of Event Scale total score and intrusion subscale. The Mississippi scale also showed a strong positive correlation with the PTSD subscale of the MMPI. The relationship between the Impact of Event Scale avoidance subscale and the Mississippi scale, although statistically significant, was considerably weaker, and the correlation of the Impact of Event Scale avoidance subscale with the PTSD subscale of the MMPI did not reach statistical

TABLE 1. Vietnam Veterans' Scores on Measures of PTSD and Correlations Between Measures

Measure	Score		Mississippi Scale for Combat-Related PTSD	Correlation (r)			MMPI PTSD Subscale	Vietnam Era Stress Inventory
	Mean	SD		Total	Intrusion	Avoidance		
SCID-R (N=102) <sup>a</sup>	10.9	3.7	0.65 <sup>b</sup>	0.48 <sup>b</sup>	0.49 <sup>b</sup>	0.32 <sup>c</sup>	0.46 <sup>b</sup>	0.31 <sup>c</sup>
Mississippi Scale for Combat-Related PTSD (N=121)	127.3	19.0	—	0.53 <sup>b</sup>	0.56 <sup>b</sup>	0.29 <sup>c</sup>	0.71 <sup>b</sup>	0.44 <sup>b</sup>
Impact of Event Scale (N=115)								
Total	55.7	10.6	—	—	0.83 <sup>b</sup>	0.80 <sup>b</sup>	0.33 <sup>b</sup>	0.19
Intrusion	27.6	6.8	—	—	—	0.32 <sup>c</sup>	0.33 <sup>b</sup>	0.19
Avoidance	28.2	6.2	—	—	—	—	0.21	0.11
MMPI PTSD subscale (N=108)	32.2	9.9	—	—	—	—	—	0.25
Vietnam Era Stress Inventory <sup>d</sup>	90.4	26.8	—	—	—	—	—	—

<sup>a</sup>Values represent the number of PTSD symptoms endorsed. SCID-R symptom total scores could not be computed for 28 patients because these patients provided unscorable responses to some symptom items. Some patients were not given or did not complete some psychometric scales because of nonsystematic exigencies in the clinical setting.

<sup>b</sup> $p < 0.001$ , two-tailed.

<sup>c</sup> $p < 0.01$ , two-tailed.

<sup>d</sup>Vietnam Era Stress Inventory items were scored on a 5-point Likert scale (range=0–4). The total score possible for the 40 items was 160.

significance. Consistent with this trend, the Impact of Event Scale avoidance subscale showed the weakest association with the SCID-R compared with all of the other psychometric indexes.

Finally, only the SCID-R and the Mississippi scale showed statistically significant positive correlations with level of combat exposure. The variance accounted for by the Mississippi scale in this correlation was over twice that explained by the correlation of the SCID-R with combat exposure (19.4% versus 9.8%).

## DISCUSSION

The Mississippi Scale for Combat-Related PTSD, the Impact of Event Scale total score and intrusion and avoidance subscales, and the PTSD subscale of the MMPI were found to be significantly correlated with degree of *DSM-III-R* PTSD symptoms, as operationalized by the SCID-R. Correlations between the SCID-R and psychometric indexes of PTSD may have been attenuated somewhat because of the restricted range of variability in subjects studied, who had high levels of combat exposure and PTSD symptoms. Nevertheless, there is substantive empirical support for the convergent validity of psychometric indexes of PTSD as continuous measures of the disorder as it varies along a dimension of severity. The evidence provided here suggests that these psychometric measures may be useful as quantitative indexes of PTSD symptom severity for clinical and research purposes.

The Mississippi scale was found to have the highest degree of association with the SCID-R among all the psychometric measures studied. This finding may reflect the fact that the Mississippi scale is the only measure designed to assess *DSM-III* PTSD symptoms in

Vietnam veterans who have been exposed to combat. The utility of the Mississippi scale, in particular, was supported as being a cost-effective means for diagnostic screening and case finding that corresponds reasonably well to a more elaborate interview method of assessment (the SCID-R). The relatively lower correlations of the Impact of Event Scale total score and subscales with the SCID-R may have occurred because the Impact of Event Scale measures a more restricted range of PTSD phenomena and was not specifically developed to assess combat-related PTSD in a Vietnam veteran population. Likewise, the correlation of the PTSD subscale of the MMPI with the SCID-R was lower than that obtained between the Mississippi scale and the SCID-R. This may have occurred because items of the PTSD subscale of the MMPI were abstracted from the MMPI rather than being originally written to assess the unique symptom profile of PTSD consistent with *DSM-III-R* criteria.

Psychometric measures of PTSD were moderately related to one another, with the exception of the Impact of Event Scale avoidance subscale. Correlations of such moderate magnitudes indicate that the instruments measure related but somewhat separate phenomena. The Mississippi scale, the PTSD subscale of the MMPI, and the Impact of Event Scale (total score and intrusion subscale) all contain items that assess intrusive sensory experiences, which may account for the positive covariation among these instruments. However, notable differences in the scope and content of PTSD-related characteristics measured by the different tests may have tempered their intercorrelation. For example, factor analysis has shown the Mississippi scale to measure dimensions other than intrusive reexperiencing and emotional numbing and/or avoidance, including interpersonal problems, emotional lability

and anger, and social alienation (4, 13). The low correlation of the Impact of Event Scale avoidance subscale with the other instruments may have resulted from the fact that its items specifically inquire about attempts to avoid intrusive affects and memories associated with traumatic events. Conversely, relatively fewer items on the SCID-R and the Mississippi scale address this phenomenon directly. Instead, these instruments focus more on other facets of the numbing and/or avoidance spectrum of symptoms (e.g., generalized emotional numbing, social estrangement, and depressive features). In any event, all of these psychometric measures assess at least part of the symptom domain of PTSD and its associated features and provide an economical means of corroborating diagnostic impressions gathered by means of interview.

The association between SCID-R symptom endorsement and level of traumatic combat exposure (the Vietnam Era Stress Inventory) was statistically significant. This finding, albeit modest, substantiates the predicted relationship between stressors and symptoms, thereby contributing to the construct validity of the PTSD diagnosis, which presumes etiological significance of stressor severity. Relative to the SCID-R and the other psychometric measures of PTSD symptoms, the Mississippi scale was most sensitive to variation in degree of combat exposure. The significant correlations of the Vietnam Era Stress Inventory with the SCID-R and Mississippi scale are consistent with well-documented findings that magnitude of combat exposure is an important predictor of PTSD symptoms (1, 8). The Mississippi scale and Vietnam Era Stress Inventory are both questionnaire methods of assessment, whereas the SCID-R uses an interview format. These differences may partially explain the relatively strong correlation between the Mississippi scale and the Vietnam Era Stress Inventory, compared with that found between the SCID-R and Vietnam Era Stress Inventory.

At this early stage of knowledge, it is probably best to use multiple indicators of PTSD symptoms, including a structured diagnostic interview to establish a categorical diagnosis, and psychometric tests to assess degree of symptom involvement on a continuum of

severity. Further research is needed to cross-validate the findings of this study on different samples of veterans who have been exposed to combat.

## REFERENCES

1. Kulka RA, Schlenger WE, Fairbank JA, et al: Contractual Report of Findings From the National Vietnam Veterans Readjustment Study, vol 1: Executive Summary, Description of Findings, and Technical Appendices. Research Triangle Park, NC, Research Triangle Institute, 1988
2. Horowitz MJ, Wilner N, Alvarez W: Impact of Event Scale: a measure of subjective stress. *Psychosom Med* 1979; 41:209-218
3. Keane TM, Malloy PF, Fairbank JA: Empirical development of an MMPI subscale for the assessment of combat-related post-traumatic stress disorder. *J Consult Clin Psychol* 1984; 52:881-891
4. Keane TM, Caddell JM, Taylor KL: Mississippi Scale for Combat-Related Posttraumatic Stress Disorder: three studies in reliability and validity. *J Consult Clin Psychol* 1988; 56:85-90
5. Schwarzwald J, Solomon Z, Weisenberg M, et al: Validation of the Impact of Event Scale for psychological sequelae of combat. *J Consult Clin Psychol* 1987; 55:251-256
6. Eysenck HJ: A critique of contemporary classification and diagnosis, in *Contemporary Directions in Psychopathology: Toward the DSM-IV*. Edited by Millon T, Klerman GL. New York, Guilford Press, 1986
7. Green B, Lindy JD, Grace MC: Posttraumatic stress disorder: toward DSM-IV. *J Nerv Ment Dis* 1985; 173:406-411
8. Laufer RS, Yager T, Frey-Wouters E, et al: *Legacies of Vietnam: Comparative Adjustment of Veterans and Their Peers*, vol 3. Washington, DC, US Government Printing Office, 1981
9. Spitzer RL, Williams JBW, Gibbon M: *Structured Clinical Interview for DSM-III-R—Patient Version*. New York, New York State Psychiatric Institute, Biometrics Research, 1987
10. Zilberg NJ, Weiss DS, Horowitz MJ: Impact of Event Scale: a cross-validation study and some empirical evidence supporting a conceptual model of stress response syndromes. *J Consult Clin Psychol* 1982; 50:407-414
11. Cannon DS, Bell WE, Andrews RH, et al: Correspondence between MMPI PTSD measures and clinical diagnosis. *J Pers Assess* 1987; 51:517-521
12. Vanderploeg RD, Sisson GFP, Hickling EJ: A reevaluation of the use of the MMPI in the assessment of combat-related post-traumatic stress disorder. *J Pers Assess* 1987; 51:140-150
13. McFall ME, Smith DE, Mackay PW, et al: Reliability and validity of the Mississippi Scale for Combat-Related PTSD. *Psychological Assessment: A Journal of Consulting and Clinical Psychology* (in press)

### Will We Save the Homeless Mentally Ill?

H. Richard Lamb, M.D.

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*Progress in alleviating the plight of the homeless mentally ill has been very slow and disappointing. After reviewing the needs of the homeless mentally ill, the author makes recommendations for immediate action. Extensive case management services should be implemented rather than simply discussed. All incompetent and/or dangerous or gravely disabled homeless mentally ill persons should be brought to hospitals, involuntarily if necessary. Cost-effective alternatives to hospitals with varying degrees of structure should be provided. Involuntary mechanisms such as conservatorship and outpatient commitment should be used when needed. The emphasis should be on timely transfer to acceptable treatment and living situations rather than waiting for the ideal.*

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There has been much discussion about but very little definitive action on behalf of the homeless mentally ill, a problem whose very existence can only be considered incredible in a modern affluent nation. My purpose here is to advocate doing what is necessary to deal expeditiously and definitively with this problem.

#### WHAT THE HOMELESS MENTALLY ILL NEED

The recommendations of APA's Task Force on the Homeless Mentally Ill (1), if implemented, would probably greatly reduce the prevalence of homelessness

among people with major mental illness. The task force saw homelessness as but one symptom of the problems besetting the chronically mentally ill generally in the United States and called for a comprehensive and integrated system of care for the chronically mentally ill to address the underlying problems that cause homelessness. Such a system would include an adequate number and range of supervised, supportive housing settings; a well-functioning system of case management; adequate, comprehensive, and accessible crisis intervention, both in the community and in hospitals; less restrictive laws on involuntary treatment; and ongoing treatment and rehabilitative services, all provided assertively through outreach when necessary.

Little has been done, however, to implement these recommendations since they were published in 1984. Some welcome exceptions are the current outreach services in New York City that include bringing patients to hospitals involuntarily, the implementation of case management strategies in some jurisdictions, and the broadening of civil commitment in some states, including outpatient commitment. Generally, when anything has been done, it has too often relied primarily on shelters. Although they are a necessary emergency resource, shelters address the symptom and do not get at the root of the problem; they are only temporary solutions from night to night.

The very fact that the homeless mentally ill are offered such facilities as shelters implies an acceptance by society of the principle that it is a basic right of the mentally ill, irrespective of their mental status and lack of competence, to refuse treatment and appropriate housing and live on the streets instead. There they live a life characterized by dysphoria and deprivation, can be victimized by any predator, and can develop life-threatening medical problems because of lack of medical intervention. Should the chronically and severely mentally ill have the right to "choose" such a life style without regard to their lack of competence to make such a decision? I think not. This is a cruel interpreta-

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tion of the basic principles of civil rights that are so important to all of us in the United States.

Even a partial implementation of the recommendations of the APA task force would make a difference. Case management is an example. In a well-functioning system of case management, every chronically mentally ill person would be on the caseload of a mental health agency that would provide assertive outreach services, have sufficient staff to work intensively with these patients, take full responsibility for individualized treatment planning, link patients to needed resources, and monitor them so that they not only receive the services they need but are not lost to the system. It is reasonable to assume that such a system of case management would result in many more chronically mentally ill persons receiving services, including housing. Moreover, much of this could be accomplished on a voluntary basis. In such a situation, the number of homeless mentally ill would undoubtedly decrease.

Can we wait still longer for this to happen? Case management has been much discussed, but in too many jurisdictions little has been done to implement it. There is every indication, especially in our larger cities, where a high proportion of the homeless mentally ill are, that not only are there insufficient funds to do this but the bureaucracies are too ponderous and inefficient (2) to set up a comprehensive and competent case management system for the homeless mentally ill even if they had the funds.

Moreover, a large proportion of the homeless mentally ill tend to be resistant to taking psychotropic medications, to treatment generally, and to accepting any living situation. For instance, in funding a large-scale program designed to help the homeless mentally ill, the state legislature of California stipulated that services funded by this program could only be voluntary. An independent evaluation of this program (3) showed that, on average, about 30% of the homeless mentally ill refused housing placements offered to them as a result of voluntary outreach case management, the primary modality of the program.

Because of their illnesses, many mentally ill individuals are unable to take advantage of living situations available to them. For instance, a recent study (4) found that some homeless mentally ill persons had places to live but were too paranoid to live there. The disabling functional deficits of major mental illness appear to be important contributing factors to homelessness among the mentally ill. These deficits include disorganized thinking and actions, poor problem-solving skills, and an inability to mobilize themselves due to depression. These are crucial deficits that should lead us to intervene, preferably with the patient's consent but without it if necessary. Still another major problem with a high proportion of the homeless mentally ill (probably two-thirds or more) is serious substance abuse problems over which these patients have little if any control.

## RECOMMENDATIONS

What then should we do? First of all, the chronically mentally ill must be our highest priority in public mental health. A large proportion of public mental health funding, now used for other activities, should be shifted to the care and treatment of the chronically mentally ill, which would, of course, include the homeless mentally ill.

We need to take action without waiting for the ideal to happen. We want to have comprehensive and coordinated mental health systems that would engage the homeless mentally ill and help many of them voluntarily accept treatment and suitable living arrangements. But the homeless mentally ill cannot wait decades for these systems to be established. Moreover, many homeless mentally ill persons will not accept services even with assertive outreach case management. In the meantime, if homeless persons with major mental illness are incompetent to make a decision with regard to accepting treatment and/or present a danger to themselves or others or are gravely disabled, then I believe that outreach teams including psychiatrists should bring all of these patients to hospitals, involuntarily if need be. No person meeting these criteria should be left living on the streets.

Do these persons have a right to live on the streets? It is my belief that the question should be phrased differently—Does society have the right to deny involuntary treatment to this population? I believe the answer is no and that these persons have a right to involuntary treatment (5, 6). Although being a danger to themselves or others or gravely disabled is a primary issue here and serves as legal and clinical grounds for depriving these persons of their "liberty," there are other fundamental questions. Are we physicians who care for the sick or are we not? Are we a caring society or are we not?

Although there has been hesitancy on the part of some professionals to use involuntary hospitalization, studies have shown that, after they have gone into remission, a large proportion of patients who had refused treatment state that their involuntary hospitalization was appropriate (7, 8).

If after a relatively brief hospitalization (a few weeks to a few months), mentally ill individuals can be placed voluntarily in a suitable living situation with built-in ongoing treatment, then we need to have these resources available. I believe that although we should have high standards for treatment and supportive housing, we cannot in good conscience leave the homeless mentally ill on the streets while we wait for such resources to be developed. In the short run we should settle for resources that are acceptable if not ideal. Moreover, cost has to be a consideration. We have to work within the limits of what society is willing to pay.

Many chronically mentally ill people also need such mechanisms as conservatorship, outpatient commitment, and payees to assist with money management, and these should be provided as long as the patient is

in need of this kind of structure in the community. By giving up a little of their liberty, many patients can remain outside of hospitals and thus retain most of their liberty.

It is important that we recognize the needs of the homeless mentally ill. We need to recognize that the great majority need supervised housing; mainstream housing where persons live alone in their own apartments and have to manage by themselves is beyond the capability of the great majority of this population. Structure is a crucial concept; the needs of the homeless mentally ill fall on a continuum from modest amounts to moderate amounts to highly structured situations. It hardly needs to be stated that psychotropic medications are crucial, including neuroleptics, antidepressants, lithium, and others.

We are probably attempting to treat many patients in the community who cannot be managed in open community settings (9). These persons have a need for structure in terms of a controlled living situation where their taking of medications is supervised and they are given as much freedom as they can handle but not more. For many, this will mean a locked setting. An active schedule of activities is for many patients another important way of providing structure.

Whether a patient needs a moderate or a high degree of structure should not be seen as an ideological issue but, rather, a clinical decision based on a pragmatic assessment of the needs of each individual patient. Does the patient have sufficient internal controls to organize himself or herself to cope with life's demands? To what degree do we need to add external structure to compensate for a lack of internal controls?

Some patients need more highly structured ongoing residential care in intermediate care facilities, such as California's locked skilled nursing facilities with special programs for psychiatric patients (10). These private sector facilities have demonstrated that good-quality care can be provided at a relatively modest cost, compared, for instance, with reopening state hospitals.

A relatively large group of patients who need highly structured 24-hour care are many of those with dual diagnoses—major mental illness and serious substance abuse problems. Probably no activity contributes more to staff burnout than trying to treat the more difficult patients with dual diagnoses in open settings.

A small but important minority of the homeless mentally ill need the highly structured setting that state hospitals provide. This should be high-quality care. But again there will be times when we cannot wait for the ideal. If funds are not available, it is more humane to place these patients in hospitals where the charts and even the staffing standards do not meet the standards of the Joint Commission on Accreditation of Healthcare Facilities than to leave these neglected human beings on the streets.

It is my belief that the time for endless (and fruitless) discussion is long past. There has been more than enough wringing of hands. The time for action is overdue. What needs to be done is abundantly clear. We need to be bold and strong of will. We must be prepared to mount a large-scale operation that will give relief to all of the homeless mentally ill. The fate of these persons with such great needs and at such great risk cannot be left in the hands of the fainthearted.

#### REFERENCES

1. Talbott JA, Lamb HR: Summary and recommendations, in *The Homeless Mentally Ill: A Task Force Report of the American Psychiatric Association*. Edited by Lamb HR. Washington, DC, APA, 1984
2. Keill SL: Politics and public psychiatric programs. *Hosp Community Psychiatry* 1985; 36:1143
3. Vernez G, Burnam MA, McGlynn EA, et al: Review of California's Program for the Homeless Mentally Disabled. Santa Monica, Calif, Rand Corp, 1988
4. Lamb HR, Lamb DM: Factors contributing to homelessness among the chronically and severely mentally ill. *Hosp Community Psychiatry* 1990; 41:301–304
5. Rachlin S: One right too many. *Bull Am Acad Psychiatry Law* 1975; 3:99–102
6. Lamb HR, Mills MJ: Needed changes in law and procedure for the chronically mentally ill. *Hosp Community Psychiatry* 1986; 37:475–480
7. Bradford B, McCann S, Merskey H: A survey of involuntary patients' attitudes towards their commitment. *Psychiatr J Univ Ottawa* 1986; 11:162–165
8. Srinivasan D, Soundarajan P, Hullin R: Attitudes of patients and relatives to compulsory admission. *Br J Psychiatry* 1980; 136:200–201
9. Lamb HR: Deinstitutionalization at the crossroads. *Hosp Community Psychiatry* 1988; 39:941–945
10. Lamb HR: Structure: the neglected ingredient of community treatment. *Arch Gen Psychiatry* 1980; 37:1224–1228

## Neuroleptic Addition in Fluvoxamine-Refractory Obsessive-Compulsive Disorder

Christopher J. McDougle, M.D., Wayne K. Goodman, M.D., Lawrence H. Price, M.D.,  
Pedro L. Delgado, M.D., John H. Krystal, M.D., Dennis S. Charney, M.D.,  
and George R. Heninger, M.D.

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*Nine of 17 patients with obsessive-compulsive disorder responded when neuroleptic was added to fluvoxamine with or without lithium. Comorbid occurrence of tic spectrum disorders or of schizotypal personality disorder was associated with response. Abnormalities in brain dopamine and serotonin may be implicated in such patients.*

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Although drug response data suggest that serotonin reuptake inhibition is critical to the treatment of obsessive-compulsive disorder, many patients with the disorder do not respond to agents that possess this effect (1). It is conceivable that this subgroup of patients has neurochemical abnormalities different from or in addition to serotonin dysregulation.

In this study, neuroleptic was added to ongoing treatment in obsessive-compulsive patients unresponsive to fluvoxamine with or without lithium. These cases were reviewed to determine whether comorbid tic spectrum disorders or schizotypal personality disorder were associated with a positive response to the addition of neuroleptic. Tic spectrum disorders were

examined because of clinical and genetic overlap between obsessive-compulsive disorder and Tourette's disorder (Tourette's syndrome) (2) and because haloperidol and pimozide are effective drugs for treating tics and Tourette's disorder (3). The presence of schizotypal personality disorder was considered because of the efficacy of low-dose neuroleptic in this disorder (4).

### METHOD

Nine inpatients and eight outpatients (10 women and seven men; mean  $\pm$  SD age =  $33.5 \pm 12.7$  years) participated in this study. All patients met *DSM-III-R* criteria for primary obsessive-compulsive disorder, and all patients gave written informed consent to participate in the study. All 17 patients had been unresponsive to a placebo-controlled trial of fluvoxamine with or without lithium. They had received placebo for 2 weeks and fluvoxamine (mean  $\pm$  SD dose =  $291 \pm 26.4$  mg/day) for a mean of  $7.7 \pm 2.3$  weeks, followed by lithium augmentation in 13 of the patients (mean dose =  $1038 \pm 155.7$  mg/day) for a mean of  $3.2 \pm 0.8$  weeks.

Criteria for lack of response to fluvoxamine with or without lithium included 1) less than 35% improvement on the Yale-Brown Obsessive-Compulsive Scale (copy available from Dr. Goodman on request), 2) no better than minimal improvement on the Clinical Global Impression (CGI) scale (5), and 3) consensus of the treating clinician and unit chiefs that the patient was unimproved. Yale-Brown Obsessive-Compulsive Scale scores had decreased only 11% (mean raw score decrease =  $3.1 \pm 4.5$ ;  $t = 2.9$ ,  $df = 16$ ,  $p < 0.01$ ) before neuroleptic addition.

Neuroleptic was added to fluvoxamine plus lithium in nine patients and to fluvoxamine alone in eight

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**TABLE 1.** Ratings of Obsessive-Compulsive Patients Before and After Addition of Neuroleptic to Fluvoxamine Treatment With or Without Lithium

		Score						
Rating Instrument	N	Baseline		After Neuroleptic		Paired t Test		
		Mean	SD	Mean	SD	t	df	p
Yale-Brown Obsessive-Compulsive Scale	15	25.1	16.9	16.1	10.0	4.0	14	<0.001
Hamilton Rating Scale for Depression	14	28.0	9.9	21.4	11.6	2.6	13	<0.02
Hamilton Rating Scale for Anxiety	14	18.7	8.6	13.5	5.5	2.5	13	<0.03

patients. Fourteen patients received pimozide (mean dose =  $6.5 \pm 5.4$  mg/day), two patients received thioridazine, 100 mg/day and 75 mg/day, respectively, and one patient received thiothixene, 6 mg/day. Neuroleptic treatment lasted 2–8 weeks (mean =  $4.7 \pm 1.9$  weeks). Except for low-dose benzodiazepines for sleep, no other drugs were administered. Formal behavior therapy was not given.

Severity of obsessive-compulsive symptoms was rated with the Yale-Brown Obsessive-Compulsive Scale. Depressive and anxiety symptoms were rated on a modified version of the Hamilton Rating Scale for Depression (24-item, obsessive-compulsive item excluded) (6) and on the Hamilton Rating Scale for Anxiety (7). Global response was assessed with the CGI, and responders were defined as “much improved” or “very much improved.”

These 17 cases of obsessive-compulsive disorder were reviewed by a rater blind to outcome to determine whether concurrent tic spectrum disorders or schizotypal personality disorder was present. Although no standardized interview was used, full syndromal expression meeting *DSM-III-R* criteria was required for a diagnosis of a tic spectrum disorder (Tourette's disorder or chronic motor or vocal tic disorder) or schizotypal personality disorder.

All statistical tests were two-tailed, with significance set at  $p < 0.05$  unless otherwise indicated.

## RESULTS

For the entire sample, addition of neuroleptic was associated with a significant decrease in scores on the Yale-Brown Obsessive-Compulsive Scale (mean  $\pm$  SD decrease =  $9.1 \pm 8.9$ ), the Hamilton depression scale ( $6.9 \pm 10.0$ ), and the Hamilton anxiety scale ( $5.4 \pm 8.2$ ) (table 1). On the basis of the CGI criterion, nine (53%) of 17 patients were judged to be responders after addition of neuroleptic to fluvoxamine with or without lithium. There was a 62% decrease in Yale-Brown Obsessive-Compulsive Scale scores for responders (mean raw score decrease =  $14.8 \pm 7.7$ ;  $t = 5.4$ ,  $df = 7$ ,  $p < 0.001$ ). T tests revealed no significant differences between responders and nonresponders in age, duration of treat-

ment with fluvoxamine with or without lithium before the addition of neuroleptic, or baseline ratings of severity on the Yale-Brown Obsessive-Compulsive Scale or the Hamilton scales. Fisher's exact tests revealed no significant differences between responders and nonresponders with regard to sex, inpatient versus outpatient status, or treatment with versus without lithium. Seven (88%) of eight patients with comorbid tic spectrum disorders or schizotypal personality disorder were responders, whereas only two (22%) of nine patients without these diagnoses were responders ( $p = 0.02$ , Fisher's exact test).

More than half of the patients experienced mild to moderate extrapyramidal side effects after the addition of neuroleptic. One patient developed dystonic symptoms requiring discontinuation of pimozide. In general, however, the combination was well tolerated.

## DISCUSSION

This open trial suggests the efficacy of neuroleptic addition in the treatment of obsessive-compulsive patients who do not respond to an adequate trial of fluvoxamine with or without lithium. Nine of the 17 patients were judged responders. Comorbid occurrence of tic spectrum disorders or schizotypal personality disorder was associated with a positive response to addition of neuroleptic. These findings generate some critical questions.

Did improvement result from fluvoxamine with or without lithium alone, neuroleptic alone, or a synergistic action of fluvoxamine with or without lithium combined with neuroleptic? In the present study, 13 patients who received lithium completed a mean 10.9-week fluvoxamine trial and four patients who did not receive lithium completed a mean 7.7-week fluvoxamine trial before the addition of neuroleptic. The lack of clinically significant change despite adequate duration of treatment (1) argues against a primary fluvoxamine effect. Moreover, response was unrelated to treatment duration. However, the study design cannot exclude the possibility that patients may have improved simply because duration of their treatment with fluvoxamine was longer.



To our knowledge, there are no controlled studies evaluating lithium augmentation in obsessive-compulsive disorder. However, even though therapeutic serum lithium levels were attained in the current study, treatment with lithium during combined fluvoxamine-neuroleptic therapy (in nine patients) did not differentiate responders from nonresponders.

Although there are reports of the successful treatment of obsessive-compulsive disorder with neuroleptic alone, most results have been disappointing (8). A direct effect of neuroleptic in our patients cannot be excluded without double-blind trials. However, because of the frequency of toxic side effects and because of the efficacy of the serotonin reuptake inhibitors, neuroleptics should not be used as the first treatment for obsessive-compulsive disorder.

The results of this study suggest that the use of neuroleptic and fluvoxamine with or without lithium may result in a greater net therapeutic effect than either treatment alone in some patients with obsessive-compulsive disorder. Given the complex interactions between dopamine and serotonin in the brain (9), the simultaneous operation of serotonin reuptake inhibition and dopamine receptor antagonism may actually yield a synergistic therapeutic effect.

Can clinical predictors of response to this combination treatment strategy be identified in obsessive-compulsive patients? This study identified tic spectrum disorders and schizotypal personality disorder as comorbid diagnoses associated with response to neuroleptic addition. Tourette's disorder has been linked to obsessive-compulsive disorder by genetic studies (2). The symptoms of Tourette's disorder are reduced with haloperidol and pimozide (3), suggesting that increased dopamine function may contribute to the pathophysiology of this disorder.

The efficacy of low-dose neuroleptic alone in treating schizotypal personality disorder has been demonstrated (4). Although Jenike et al. (10) reported that comorbid obsessive-compulsive disorder and schizotypal personality disorder were predictive of a poor response to both pharmacotherapy and behavior therapy, it is unlikely that systematic trials of combined neuroleptic and serotonin reuptake inhibitor were used in their "schizo-obsessive" patients.

In summary, a time-limited trial of neuroleptic addition, with reassessment at regular intervals, may be warranted in patients with severe, treatment-refractory obsessive-compulsive disorder. However, because of the toxicity associated with neuroleptics, adequate trials of serotonin reuptake inhibitors (e.g., fluvoxamine, fluoxetine, clomipramine) should be completed before this coactive strategy is used. Further research is required to confirm these findings and to determine whether clinical predictors of treatment response can be identified prospectively. These data suggest that with some obsessive-compulsive patients, both the serotonin and dopamine systems may be involved in the mediation of obsessive-compulsive symptoms.

#### REFERENCES

1. Goodman WK, Delgado PL, Price LH, et al: Fluvoxamine versus desipramine in OCD, in New Research Program and Abstracts, 142nd Annual Meeting of the American Psychiatric Association. Washington, DC, APA, 1989
2. Pauls DL, Towbin KE, Leckman JF, et al: Gilles de la Tourette's syndrome and obsessive-compulsive disorder: evidence supporting an etiological relationship. *Arch Gen Psychiatry* 1986; 43: 1180-1182
3. Shapiro E, Shapiro AK, Fulop G, et al: Controlled study of haloperidol, pimozide, and placebo for the treatment of Gilles de la Tourette's syndrome. *Arch Gen Psychiatry* 1989; 46:722-730
4. Hymowitz P, Frances A, Jacobsberg LB, et al: Neuroleptic treatment of schizotypal personality disorders. *Compr Psychiatry* 1986; 27:267-271
5. Guy W: ECDEU Assessment Manual for Psychopharmacology: Publication 76-338. Washington, DC, US Department of Health, Education, and Welfare, 1976
6. Mazure C, Nelson JC, Price LH: Reliability and validity of the symptoms of major depressive illness. *Arch Gen Psychiatry* 1986; 43:451-456
7. Hamilton M: The assessment of anxiety states by rating. *Br J Med Psychol* 1959; 32:50-55
8. Jenike MA: Somatic treatments, in *Obsessive-Compulsive Disorders: Theory and Management*. Edited by Jenike MA, Baer L, Minichiello WE. Littleton, Mass, PSG, 1986
9. Korsgaard S, Gerlach J, Christensson E: Behavioral aspects of serotonin-dopamine interaction in the monkey. *Eur J Pharmacol* 1985; 118:245-252
10. Jenike MA, Baer L, Minichiello WE, et al: Concomitant obsessive-compulsive disorder and schizotypal personality disorder. *Am J Psychiatry* 1986; 143:530-532

# Lithium Treatment for Cocaine Abusers With Bipolar Spectrum Disorders

Edward V. Nunes, M.D., Patrick J. McGrath, M.D.,  
Steven Wager, M.D., and Frederic M. Quitkin, M.D.

*An open trial of lithium carbonate showed little efficacy for 10 cocaine abusers with bipolar spectrum disorders. It may be that the bipolar subgroup of cocaine abusers is heterogeneous and that only a fraction are lithium responsive.*

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Although hypothesized to have cocaine antagonist properties (1, 2), lithium proved no different from placebo and inferior to desipramine as a treatment for unselected cocaine abusers in a recent controlled trial (3). Nevertheless, the results of one small open trial (N=9) suggest that lithium might be effective in the subgroup of cocaine abusers with putative bipolar spectrum disorders, who may be self-medicating (4). We report a second open trial of lithium for 10 cocaine abusers with bipolar spectrum disorders.

## METHOD

The subjects were 10 consecutive patients seeking treatment for cocaine dependence at our university-based outpatient clinic who also met the *DSM-III-R* criteria for a bipolar disorder. The patients were evaluated by experienced research psychiatrists using a *DSM-III-R* checklist. Affective disorder was diagnosed only if its onset preceded the onset of all substance dependence disorders during the patient's lifetime. The bipolar disorders were characterized by hypomania (bipolar disorder not otherwise specified) (patients 3-

6, 9, 10) or cyclothymia (patients 1, 2, 7, 8). There were no histories of full mania. Five patients met the lifetime criteria for major depression (patients 3, 4, 8, 9) or dysthymic disorder (patient 2), and seven had lifetime histories of alcohol dependence (patient 7), other drug dependence (patients 5, 10), or both (patients 1, 4, 6, 9). Five of the 10 (patients 1-4, 10) each had at least one first-degree relative with alcoholism. There were no clear-cut family histories of affective disorder, although the mothers of two patients (patients 6, 7) were described as "moody," and the mother of a third (patient 1) had had a "nervous breakdown" of unknown type.

The sample included eight men and two women. Five were white, three were black, and two were Hispanic. Four were unemployed. The mean  $\pm$  SD age was  $34 \pm 4$  years. The mean  $\pm$  SD age at onset of cocaine dependence was  $27 \pm 7$  years, and the age at onset of first substance dependence was  $21 \pm 5$  years. Four used cocaine intranasally, one injected it intravenously, and five used freebase cocaine or crack. The average amount of cocaine used over the past year was  $4.1 \pm 3.7$  g/week (range=1.0-13.0). The mean baseline score on the Hamilton Rating Scale for Depression was in the mildly depressed range ( $7.7 \pm 5.4$ ). Only three patients (patients 3, 8, 9) had baseline scores higher than 10.

Each patient met weekly with a research psychiatrist and a drug counselor. Participation in Cocaine Anonymous or Narcotics Anonymous was urged. After giving informed consent, the patients received placebo for 1 week on a single-blind basis and were then openly given lithium carbonate. The trial was intended to last 12 weeks, but before that time six patients dropped out and one was removed because of nonresponse. However, eight patients received lithium for 6 or more weeks and had blood levels between 0.4 and 1.0 meq/liter.

Each week the patients were asked to report cocaine use, to complete the Cocaine Craving Scale (4) and the Cocaine High Scale (20 points each, based on 100-mm line), and to provide urine samples for determination of cocaine use. The Hamilton scale and the 28 hypomania and biphasic items of the General Behavior Inventory (5) were administered biweekly. The General

Received March 29, 1989; revision received Oct. 3, 1989; accepted Oct. 31, 1989. From the Depression Evaluation Service and the Department of Therapeutics, New York State Psychiatric Institute, and the Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York. Address reprint requests to Dr. Nunes, Depression Evaluation Service, New York State Psychiatric Institute, Box 35, 722 West 168th St., New York, NY 10032.

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TABLE 1. Response to Lithium of 10 Consecutive Cocaine Abusers With Bipolar Spectrum Disorders

Patient	Age (years)	Race	Sex	Route of Adminis- tration	Lithium Trial			Comments
					Dose (mg/day)	Blood Level (meq/liter)	Length (weeks)	
Nonresponders <sup>a</sup>								
1	34	White	M	Intravenous	600	0.1	3	Craving and mood unchanged
2	33	White	M	Free-base	600	—	3	Craving and mood unchanged; com- plaints of sedation
3	32	White	F	Intranasal	1500	1.0	12	Craving and hypomania better; de- pression worse <sup>b</sup>
4	33	White	M	Free-base	900	0.7	8	Craving better; mood unchanged
5	40	Black	M	Free-base	600	0.4	6	Craving unchanged; mood better; complaints of sedation
6	31	Hispanic	M	Free-base	900	0.8	8	Craving unchanged; mood better; complaints of sedation
7	30	White	M	Intranasal	1200	0.7	7	Craving unchanged; mood depressed, "too even," "miss the highs" <sup>c</sup>
Responders <sup>a</sup>								
8	32	Black	F	Intranasal	600	0.6	12	Craving and mood better; sustained remission
9	41	Black	M	Free-base	1200	0.8	9	Craving better; depression and alcohol abuse unchanged
10	32	Hispanic	M	Intranasal	1500	0.7	12	Craving better; hyperthymia un- changed; stopped taking lithium and relapsed

<sup>a</sup>Response defined as 3 consecutive cocaine-free weeks, confirmed by urine screening.

<sup>b</sup>Subsequently improved with imipramine.

<sup>c</sup>Subsequently improved with fluoxetine.

Behavior Inventory is rated by the patient; the possible raw scores range from 28 to 112.

A favorable clinical response was defined as 3 consecutive weeks of abstinence from cocaine, confirmed by urine screening, at any time during the trial. Mean changes from baseline to endpoint for cocaine use, craving, Hamilton score, and General Behavior Inventory hypomania score were tested with two-tailed paired *t* tests.

## RESULTS

Most patients showed some reduction in cocaine use, but the mean decrease ( $0.74 \pm 1.63$  g/week) was not statistically significant ( $t=1.32$ ,  $df=8$ ). As shown in table 1, only three of the 10 patients (patients 8–10) were cocaine free for 3 consecutive weeks. One of these (patient 9) had persistent depression and alcohol abuse and dropped out at week 9, and another (patient 10) stopped taking lithium and relapsed just after week 12. Only one (patient 8) achieved sustained cocaine abstinence.

Five patients (patients 3, 4, 8–10) had some reduction in craving, although the mean decrease ( $2.6 \pm 5.2$ ) was not significant ( $t=1.58$ ,  $df=9$ ). Only one patient showed a decrease in cocaine euphoria (patient 8). Mood, particularly hypomania, was improved in five patients (patients 3, 5–8). The mean reduction in the scores on the General Behavior Inventory hypomania items neared significance ( $13.7 \pm 19.3$ ;  $t=2.13$ ,  $df=8$ ,  $p<0.10$ ). The mean reduction in Hamilton scores was slight ( $1.1 \pm 6.2$ ;  $t=0.56$ , *n.s.*). Persistent depression

(patients 3, 7, 9) and complaints of sedation (patients 2, 5, and 6) were common.

## DISCUSSION

Lithium showed little efficacy in our sample of bipolar cocaine abusers. The 30% response rate resembles that of the lithium and placebo groups in Gawin et al.'s controlled trial, which were not selected for bipolarity (3). Further, two responses were transient. Only one patient achieved a stable remission. We were thus unable to replicate Gawin and Kleber's favorable experience with lithium in nine cyclothymic cocaine abusers (4). Several factors might explain this discrepancy.

Our small sample size increases the likelihood of a type II error (i.e., false conclusion of lack of efficacy). Thus, further study with larger samples is needed.

The majority of the patients in our sample were intravenous or freebase users and five belonged to racial/ethnic minorities, variables that may be associated with poor compliance or outcome (6). Nevertheless, the trial lengths and lithium blood levels were adequate for eight of the 10 patients.

The high prevalence of past and family histories of alcoholism in these patients was also found among the bipolar subjects in our previous study (7). These patients may have alcoholic rather than bipolar diatheses. Their mood swings may be caused by alcohol or drugs, resulting in misdiagnosis despite our attempt to historically identify antecedent affective disorder. A related problem is that hypomanic and cyclothymic syndromes have shown poor diagnostic reliability (8). We

did not test reliability, but all diagnoses were discussed and agreed on by consensus at our clinical staff meeting.

The absence of full manic syndromes and of family history of mania suggests that our patients may not have had bipolar I mood disorders. Family history data suggest that patients with bipolar II disorder are heterogeneous, containing a subgroup with bipolar I disorder, a unipolar subgroup, and a subgroup of bipolar II patients that "breeds true" (9). The latter may respond well to antidepressants alone (10). Two patients with persistent depression despite lithium treatment subsequently improved while taking antidepressants, as did another cocaine abuser with bipolar spectrum disorder, who came to us after failing to respond to lithium. A related issue is that these patients may consider sedation or loss of hypomania unwelcome; patient 7 complained he felt "too even" and missed the "highs."

In summary, we suspect that cocaine abusers whose symptoms suggest bipolar spectrum disorders are heterogeneous and that only a fraction will respond to lithium. The failure of our sample to respond to lithium may have no relevance to cocaine abusers with bipolar I disorder. When depressive symptoms predominate, antidepressant medication might be tried as an adjunct to counseling in this group.

## REFERENCES

1. Mandell AJ, Knapp S: Asymmetry and mood, emergent properties of serotonin regulation: a proposed mechanism of action of lithium. *Arch Gen Psychiatry* 1979; 36:909-916
2. Post RM, Weiss RB, Pert A: Differential effects of carbamazepine and lithium on sensitization and kindling. *Prog Neuropsychopharmacol Biol Psychiatry* 1984; 8:425-434
3. Gawin FH, Kleber HD, Byck R, et al: Desipramine facilitation of initial cocaine abstinence. *Arch Gen Psychiatry* 1989; 46:117-121
4. Gawin FH, Kleber HD: Cocaine abuse treatment: open pilot trial with desipramine and lithium carbonate. *Arch Gen Psychiatry* 1984; 41:903-909
5. Depue RA, Slater JF, Wolfstetter-Kausch H, et al: A behavioral paradigm for identifying persons at risk for bipolar depressive disorder: a conceptual framework and five validation studies. *J Abnorm Psychol* 1981; 90:381-437
6. Agosti V, Nunes E, Stewart JW, et al: Patient factors related to early attrition from an outpatient cocaine research clinic. *Int J Addict* (in press)
7. Nunes EV, Quitkin FM, Klein DF: Psychiatric diagnosis in cocaine abuse. *Psychiatry Res* 1989; 28:105-114
8. Andreasen NC, Grove WM, Shapiro RW, et al: Reliability of lifetime diagnosis: a multicenter collaborative perspective. *Arch Gen Psychiatry* 1981; 38:400-405
9. Coryell W, Endicott J, Reich T, et al: A family study of bipolar II disorder. *Br J Psychiatry* 1984; 145:49-54
10. Kupfer DJ, Carpenter LL, Frank E: Possible role of antidepressants in precipitating mania and hypomania in recurrent depression. *Am J Psychiatry* 1988; 145:804-808



## Patterns of Depressive Symptoms in Expectant and New Parents

Valerie D. Raskin, M.D., Judith A. Richman, Ph.D., and Cheryl Gaines, M.D.

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*Depressive symptoms were assessed in 86 couples during pregnancy and after childbirth. Although 59.3% (N=51) of the couples contained at least one symptomatic spouse during the transition to parenthood, both spouses were symptomatic in only 11.1% (N=4) of the affected couples during pregnancy and 12.5% (N=4) after childbirth.*

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Although the birth of a child has been linked with greater negative mental health consequences for women than for men (1), the emotional impact on new fathers has received increasing attention (2). If the birth of a child is distressful for both men and women, an important question is the extent to which child-related distress in one member of a couple is shared by the other. Unfortunately, studies of the psychology of new parents often recruit husbands and wives separately (3) or exclude fathers altogether. The few studies of married couples during the transition to parenthood have compared groups of new fathers and mothers without considering the impact of one spouse's distress on the other (4).

Although careful studies of assortative mating have found little evidence of the phenomenon in affective disorders (5), there are several reasons that one might expect to find parallel levels of distress in spouses undergoing the transition to parenthood. In one study (6), severe psychopathology was found in two-fifths of husbands whose wives were admitted to the hospital

for postpartum psychiatric illness, and the wife's psychiatric illness was hypothesized to be a possible etiologic factor in the husband's psychiatric illness. A study of couples undergoing treatment for infertility found that in one-third of distressed couples, both members were symptomatic, suggesting that for many couples shared stressors in the quest for parenthood may result in shared levels of distress (B.J. Berg, unpublished manuscript, 1989). Finally, spouses' assessments of marital satisfaction are significantly correlated during the transition to parenthood (7).

To the extent that marital satisfaction may influence and be influenced by mood, depressive symptoms in new mothers and fathers might also be expected to be significantly correlated. However, to our knowledge, depressive symptoms in the couple as a unit of analysis have not been studied during the transition to parenthood. We undertook to describe patterns of depressive symptoms in couples during late pregnancy and the postpartum period. Our hypothesis was that members of couples would experience comparable symptoms during the time covered by the study. We anticipated that having an affected spouse during a period of great psychosocial stress would be a risk factor for being distressed oneself.

### METHOD

One hundred six married, physically healthy adult couples experiencing their first pregnancies were recruited by us from childbirth preparation classes. Eighty-one percent (86 couples) completed the study. Only couples in which both members completed the study were included in the analysis. No significant differences in depressive symptoms at the first assessment between subjects who failed to complete the study and those who did were found.

The study sample was mostly white (84.9%, N=73) and well educated (57.0% [N=49] of the male subjects and 69.8% [N=60] of the female subjects were college graduates). The mean  $\pm$  SD age was 31.0  $\pm$  5.6 years for the men and 29.3  $\pm$  5.1 years for the women.

Depressive symptoms were measured by the Center for Epidemiologic Studies Depression Scale (CES-D Scale) (8), administered at the 34th week of pregnancy and again 8 weeks after the birth of the child. Data

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reported here include assessments of the same couples at both time periods. Spouses were asked to complete their surveys independently.

The CES-D Scale is a 20-item self-report depression rating scale; a score higher than 16 is used to delineate "cases" of depression (9). Although clinical depression cannot be diagnosed by this or other self-report surveys, we employ this widely used cutoff point to differentiate subjects with depressed mood from those with nondepressed mood. Individuals were classified and will hereafter be referred to as "dysphoric" if their total scores equaled or exceeded 16. Couples were classified as "both dysphoric" if both members had scores of 16 or greater, "wife only" or "husband only" if only one member had a score of 16 or greater, or "both nondysphoric" if both had scores under 16. CES-D Scale scores were analyzed by Pearson coefficients to evaluate whether spouses' scores were significantly correlated.

## RESULTS

During pregnancy, in 58.1% (N=50) of the 86 couples neither spouse was depressed, in 37.2% (N=32) one spouse only was depressed, and in 4.7% (N=4) both spouses were depressed. The couples with one dysphoric spouse during pregnancy included 20 wife-only configurations (23.3% of all couples) and 12 husband-only configurations (14.0% of all couples). During the postpartum period, in 62.8% (N=54) of the couples neither spouse was depressed, in 32.6% one spouse only was depressed (N=28, 14 each of wife only and husband only), and in 4.7% (N=4) both spouses were depressed.

Although at each time point a majority of the couples were not dysphoric, in only 40.7% (N=35) of the couples were both spouses without dysphoric mood throughout the transition to parenthood. The remaining 51 couples (59.3%) had at least one dysphoric spouse during pregnancy, after the birth of the child, or throughout the study period. However, only one (1.2% of the total) of the four couples "both dysphoric" during the pregnancy was also "both dysphoric" during the postpartum period.

Of the couples in which there was an affected spouse, only 11.1% at the first assessment and 12.5% at the second contained two depressed spouses (table 1). Pearson correlation coefficients revealed no significant correlation between husbands' and wives' scores during pregnancy ( $r=0.09$ ,  $df=85$ ) or in the postpartum period ( $r=0.05$ ,  $df=85$ ).

## DISCUSSION

Our findings show a consistent but unexpected pattern in couples' distress during the transition to parenthood: when one member of a couple is dysphoric, the other is unlikely to be similarly affected. This pat-

**TABLE 1. Presence of Dysphoric Mood<sup>a</sup> in 86 Couples During Pregnancy and After the Birth of the First Child**

	After 34 Weeks of Pregnancy			8 Weeks After Birth of Child		
		Spouse Also Dysphoric <sup>a</sup>			Spouse Also Dysphoric <sup>a</sup>	
Dysphoric Spouse	N	N <sup>b</sup>	%	N	N <sup>b,c</sup>	%
Husband	16	4	25.0	18	4	22.2
Wife	24	4	16.7	18	4	22.2
Either spouse	36	4	11.1	32	4	12.5

<sup>a</sup>Score of 16 or more on the Center for Epidemiologic Studies Depression Scale (CES-D Scale).

<sup>b</sup>Ns in this column include the same couples.

<sup>c</sup>In one of the couples, both husband and wife were dysphoric during the pregnancy also.

tern can be called complementary, with spouses balancing divergent levels of depressive symptoms during the period studied.

The finding that nearly three-fifths of the couples had at least one member who was symptomatic either late in the pregnancy or after the birth of the child suggests that limiting one's focus to postpartum depression in women seriously underestimates the psychological distress associated with this phase of the life cycle (2). Given the recent findings of the impact of depressed mood on mother-child interactions (10), we are pleased to note that our data suggest that neonates who have one dysphoric parent are also likely to have one intact parent. However, it remains unknown whether the presence of dysphoria in a new mother or father leads to changes in the other parent's caretaking functions.

Several other questions remain unanswered. Do the spouses of depressed expectant and new parents have a greater frequency of nonaffective symptoms, such as anxiety, somatization, or substance use? Alternatively, does the presence of dysphoria in one's partner during the transition to parenthood facilitate one's coping in order to meet the demands on a parent by a newborn? If so, are these patterns of depressive symptoms present in couples at other times of shared stress?

## REFERENCES

1. Kumar R, Robson KM: A prospective study of emotional disorders in childbearing women. *Br J Psychiatry* 1984; 144:35-47
2. Osofsky H: Expectant and new fatherhood as a developmental crisis. *Bull Menninger Clin* 1982; 46:209-230
3. Gerson MJ: The prospect of parenthood for women and men. *Psychol of Women Quarterly* 1986; 10:49-62
4. Quadagno DM, Dixon LA, Denney NW, et al: Postpartum moods in men and women. *Am J Obstet Gynecol* 1986; 154: 1018-1023
5. Gershon ES, Mark A, Cohen N, et al: Transmitted factors in the morbid risk of affective disorders: a controlled study. *J Psychiatr Res* 1975; 12:283-299
6. Harvey I, McGrath G: Psychiatric morbidity in spouses of women admitted to a mother and baby unit. *Br J Psychiatry* 1988; 152:506-510
7. Belsky J, Lang ME, Rovine M: Stability and change in marriage across the transition to parenthood: a second study. *J Marriage*

- and the Family 1985; 47:855-865
8. Radloff LS: The CES-D Scale: a new self-report depression scale for research in the general population. *Applied Psychol Measurement* 1977; 1:385-401
  9. Weissman MM, Sholomskas D, Pottenger M, et al: Assessing depressive symptoms in five psychiatric populations: a validation study. *Am J Epidemiol* 1977; 106:203-214
  10. Gordon D, Burge D, Hammen C, et al: Observations of interactions of depressed women with their children. *Am J Psychiatry* 1989; 146:50-55

# Autoantibodies to Brain Lipids in Schizophrenia

Anthony L. Pelonero, M.D., Anand K. Pandurangi, M.D., and Vincent P. Calabrese, M.D.

*Serum IgG antibody to brain lipids was measured with an ELISA technique in 38 schizophrenic patients and 22 normal subjects. There were no significant differences between groups. The authors discuss methodological differences between this study and studies with positive findings.*

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For decades an autoimmune process has been postulated as a possible etiology of schizophrenia. A current theory holds that autoimmunity in schizophrenia is an aberrant immunological response to a viral infection (1). Many investigators have sought laboratory evidence of an autoimmune process, including identification of antibody to brain tissue. However, the reports on autoantibodies in persons with schizophrenia are contradictory. DeLisi et al. (2) have reviewed the work done in this area. Most recently, Heath et al. (3) have reported IgG antibody to the septal region of the brain in unmedicated schizophrenic patients.

The methods used to detect antibody have improved over the years; earlier studies used indirect hemagglutination inhibition and complement fixing, which are less sensitive than current techniques (4, 5). Enzyme-linked and radioimmunoassay techniques have been used widely for immunodiagnosis. The enzyme-linked immunosorbent assay (ELISA) is a well-established procedure for antibody determination that has gained wide acceptance. The ELISA can detect small amounts of antibody and antibody that would not be detected with other methods (6, 7).

Prior studies have used brain antigen prepared from homogenate brain, which is antigenically less specific

than purified lipids. The lipids GM-1 ganglioside and cerebroside enrich the synaptosome and membrane, respectively. Rick et al. (8) have reported behavioral changes in rats after exposure to antiganglioside antibodies, lending animal model support for an autoimmune model of psychiatric disturbance. On the basis of the theory that neuronal dysfunction in schizophrenia is secondary to the binding of antibodies to these lipids, we hypothesized that the serum level of antibodies to these specific lipids would be higher in schizophrenic patients than in matched normal control subjects. The results reported here are a test of that hypothesis.

## METHOD

The subjects consisted of 38 patients who were systematically assessed and given research diagnoses of chronic or subchronic schizophrenia (*DSM-III-R*) by one of us (A.L.P. or A.K.P.). Their mean age was 30 years (range, 20-47); 27 were men and 11 were women. The mean duration of illness was 8.7 years (range, 6 months to 20 years). Seventeen subjects were outpatients, and 21 were inpatients from acute admissions units. None of the subjects was medically ill, mentally retarded, or pregnant. All of the subjects were medicated with neuroleptics at the time of blood drawing, and all subjects gave informed consent before participating.

Twenty-two volunteer control subjects were recruited from hospital personnel and screened with a modified Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) to rule out psychiatric morbidity. All control subjects were medically healthy and matched by age, sex, and race to the patient group; all worked in the hospital environment (e.g., clerks, students, nurses).

For each subject, 20 ml of blood was collected from a forearm vein, and serum was separated within 1 hour by centrifugation, then stored in aliquots at  $-70^{\circ}\text{C}$  until assayed. An indirect microplate ELISA method (7) was used to determine absorbance of color reaction by substrate, which is a reflection of concentration of antibody bound to antigen. Color reaction is measured spectrophotometrically by an automated ELISA reader (Flow Multiskan ELISA Reader) to determine the optical density. In addition to testing matched control subjects, we tested serum samples in culture media without antigen ("blanks") to control for absorbance of

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antibody to substances in the culture media unrelated to the antigen. To test the effect of neuroleptics on the ELISA, testing of 10 control sera was done after haloperidol and thiothixene had been added in amounts sufficient to yield final concentrations of 10 ng/ml. Microplates with flat-bottom wells were used for the ELISA. All samples were assayed in duplicate on separate microplates on different days, and the average absorbance value was used in the statistical analysis. The lipid antigens used on the microplate, cerebroside, and GM-1 ganglioside were obtained commercially (Sigma Chemical Corp., St. Louis).

## RESULTS

There was no significant effect of medication on the assay for the control sera tested ( $r$  values=0.96–0.98). The antibody absorbance data were nonnormally distributed and a Wilcoxon signed rank test of the 22 paired groups was performed. There were no significant antibody absorbance differences for the antigens tested between the patients and control subjects (ganglioside sign-rank=1.5,  $p<0.96$ ; cerebroside sign-rank=-22.5,  $p<0.48$ ).

Of the 38 schizophrenic patients, two (5%) had ganglioside antibody absorbance greater than two standard deviations past the control mean; for cerebroside, one value (3%) was greater than two standard deviations beyond the control mean. One control subject's cerebroside antibody absorbance was beyond two standard deviations of the mean. These three subjects had no distinguishing characteristics. The median and range of the patients' values were as follows: ganglioside median absorbance=0.138, range=0.088–0.591; cerebroside median absorbance=0.304, range=0.190–0.741. For the control subjects they were as follows: ganglioside median absorbance=0.139, range=0.061–0.625; cerebroside median absorbance=0.333, range=0.195–1.279.

## DISCUSSION

Interpreting the results in this study with reference to previous studies is difficult because of the varied methods used, the different antigens studied, and the different types of immunoglobulins measured. The negative results of this study contradict the positive findings reported in the literature. DeLisi et al. (2) found greater IgG binding to brain membrane in psychiatric inpatients than in normal subjects, and Kelly et al. (9) found no differences between antibrain antibody in the sera of schizophrenic patients and normal control subjects. Recently, Heath et al. (3) reported detection of IgG antibody to septal region homogenate in patients before medication but not after treatment with neuroleptics. Heath et al. took measures to con-

centrate serum antibody rather than dilute the serum, as is conventional.

There are a number of limitations to this study. The control group used for an immunological study is an important consideration that has received little attention in most studies of this kind. In the present study, the control subjects were unrelated to the test subjects and were not strictly matched by socioeconomic class. However, we felt it was important that the control subjects be exposed to the same environment as the patients, and this objective was achieved by using hospital workers. The fact that our patients were medicated and tested in only one phase of illness (some in a stable nonpsychotic state, others during recovery from an acute psychosis) is a limitation of the study if antibody titers are phase dependent. CSF was not sampled and may be a better fluid to study.

The implications of testing specific brain antigens versus homogenate brain are intriguing; brain homogenate is felt to have less antigenic sensitivity and may be a major limitation of the technique used in many earlier studies. Since the antigenic materials adhere to the ELISA plate by mass action, the amount that can adhere is finite; it stands to reason that brain homogenates would yield a lower concentration of specific antigen than pure antigen. Only two specific lipids were tested as antigens in this study; other brain antigens might yield positive results. In a related study (10) we found a subgroup of schizophrenic patients with significantly higher IgG titers to herpes simplex than normal subjects.

## REFERENCES

1. Pert CB, Knight JG, Markwell MAK: Scenarios for a viral etiology of schizophrenia. *Schizophr Bull* 1988; 14:243–247
2. DeLisi LE, Weber RJ, Pert CB: Are there antibodies against brain in sera from schizophrenic patients? review and prospectus. *Biol Psychiatry* 1985; 20:110–115
3. Heath RG, McCarron KL, O'Neil CE: Antiseptal brain antibody in IgG of schizophrenic patients. *Biol Psychiatry* 1989; 25:725–733
4. Pandey RS, Gupta AK, Chaturvedi UC: Autoimmune model of schizophrenia with special reference to antibrain antibodies. *Biol Psychiatry* 1981; 16:1123–1136
5. Fessel WJ: The "antibrain" factors in psychiatric patients' sera, I: further studies with a hemagglutination technique. *Arch Gen Psychiatry* 1963; 8:614–621
6. Voller A, Bidwell D, Bartlett A: Microplate enzyme immunoassays for the immunodiagnosis of virus infections, in *Manual of Clinical Immunology*. Edited by Rose NR, Friedman H. Washington, DC, American Society for Microbiology, 1976
7. Calabrese VP, Wallen W, Castellano G, et al: Enzyme-linked immunosorbent assay (ELISA) for antibodies to human myelin and axolemma-enriched fractions. *Neurosci Lett* 1981; 21:189–195
8. Rick JT, Gregson AN, Leibowitz S, et al: Behavioral changes in adult rats following administration of antibodies against brain gangliosides. *Dev Med Child Neurol* 1980; 22:719–724
9. Kelly RH, Ganguli R, Rabin BS: Antibody to discrete areas of the brain in normal individuals and patients with schizophrenia. *Biol Psychiatry* 1987; 22:1488–1491
10. Pelonero AL, Pandurangi AK, Calabrese VP: Viral antibodies in schizophrenia using the indirect ELISA method (abstract). *Schizophr Res* 1989; 2:171

## Book Forum

Nancy C. Andreasen, M.D., Ph.D., Editor

### SLEEP AND DREAMING

*Sleep '86: Proceedings of the 8th European Congress on Sleep Research*, edited by W.P. Koella, F. Obal, H. Schulz, and P. Visser. New York, Gustav Fischer Verlag (VCH Publishers), 1988, 466 pp., \$160.00.

The problem with *Sleep '86* is that, in a rapidly moving field, it reports papers given in 1986 and published in 1988. The book includes the Hess-prize-winning paper on napping by Scott Campbell and J. Zulley, which shows sleep to be polyphasic. It also includes three special overview lectures and 138 other papers, most of them very brief, covering a wide gamut of topics. These topics include information processing in sleep, phylogeny, new hypnotics, depression, epidemiology of sleep disorders, memory, neurochemistry, and circadian and ultradian rhythms, to name a few.

The three special lectures are very good summary statements on important topics. Borbely reviews the good and bad sides of the benzodiazepines for promoting sleep and reiterates the continuing need for a natural sleep inducer. Oswald surveys the evidence that sleep repairs or promotes anabolism and that sleep deprivation impairs restoration. He makes a convincing case. Parmeggiani's review of the evidence for where sleep originates in the brain tells us that we do not yet know, that it is too complex.

Although the book is full of contradictory studies with small numbers of subjects, there is evidence of some growing consensus. Broughton's model of a "circasemidian" sleep rhythm is in concert with the data from Scott Campbell's napping study, and Horne's paper on two types of sleep (obligatory sleep and optional sleep) begs to be integrated with the chapter on the two-process model by Dijk et al. It can be seen clearly from this volume that the thinking about the "hows" and "whys" of sleep is becoming more interesting and more complex. This is especially evident in the area of REM sleep abnormalities in depressive illness. Here we learn that a shortened REM latency is and is not specific to individuals with affective disorders and some of the reasons supporting each position. We also learn that sleep abnormalities in depression are either state-like or trait-like, that mood becomes more dysphoric from dream to dream, and that few REM periods of the depressed yield any dream reports at all. In other words, this is a field still in need of much basic work before we have good agreement on sleep functioning and malfunctioning and what manipulations are helpful in promoting healthful sleep without creating problems with healthful waking. (The benzodiazepines, for example, promote rapid sleep onset in the nighttime but are followed by increases in waking anxiety.)

This book cannot serve as a text but provides a look at where we are. It contains preliminary data and speculations that raise the questions needing further clarifying work. It is in this way a gold mine for young investigators looking for problems. In addition, it is delightful to read papers from such a wide group of investigators and to see how similar

problems, like the thermoregulation function of sleep, are being approached by different groups in different countries.

ROSALIND D. CARTWRIGHT, PH.D.  
Chicago, Ill.

*Sleep*, by J. Allan Hobson. New York, Scientific American Library (W.H. Freeman and Co., distributor), 1989, 206 pp., \$32.95.

It is often difficult for scholars or scientists to write in a way that makes their fields accessible to the intelligent lay reader or to colleagues not well versed in the discipline. In *Sleep*, Professor Hobson, who is both a psychiatrist and a distinguished basic sleep researcher, succeeds in presenting a lucid, engaging, informative, and at times humorous account of modern basic sleep research. With considerable aplomb, Hobson draws on a wide-ranging knowledge of neurophysiology, biological rhythms, neuroanatomy, and psychoanalysis to offer the general reader a spectacular and highly personal overview of investigations into the sleeping brain.

This book succeeds not only because of its text, however. Perhaps among the best I have ever seen, its photographs of sleeping animals and sleeping humans, together with its scientific schematics, enhance its value for teaching and learning.

*Sleep* also offers much to the psychiatric reader interested in biological rhythms, in sleep neurophysiology (viewed developmentally and in relation to health and illness), and in the relationship of dreaming to brain function during sleep. In this last context, Hobson expounds the controversial activation-synthesis hypothesis of dreaming, initially published by Hobson and his colleague Robert McCarley in 1977 (1). Using a recent dream of his own (he calls it "a phallic tango"), Hobson argues that the formal characteristics of dreams could be adequately explained by the distinctive operational characteristics of the REM sleep state, without invoking such psychoanalytic constructs as "censoring."

*Sleep* is timely also from the viewpoint of basic neuroscience. In recent years, sleep research has become (to its detriment) increasingly a clinical enterprise, making many contributions to the developing field of sleep disorders medicine. (In this context, Hobson unfortunately does not offer an up-to-date overview of sleep disorders. This is, I think, the one major failing of *Sleep*.) Hobson reminds us, however, that investigations into the sleeping brain are central to the mission of basic neuroscience. Although we cannot be entirely sure yet of the functions of sleep, there is much evidence that sleep serves a twofold purpose—"to conserve energy and to organize information" (p. 203). Hobson concludes that "learning exactly how these functions are served is now the major agenda of sleep science" (p. 203). This is a plausible conclusion, with considerable ramifications for further understanding the relation of alterations of sleep to the pathogenesis of mental disorders.

## REFERENCE

1. Hobson JA, McCarley RW: The brain as a dream state generator: an activation-synthesis hypothesis of the dream process. *Am J Psychiatry* 1977; 134:1335-1348

CHARLES F. REYNOLDS III, M.D.  
 Thousand Island Park, N.Y.

**Dream Life, Wake Life: The Human Condition Through Dreams**, by Gordon G. Globus. Albany, State University of New York Press, 1987, 196 pp., \$34.50; \$14.95 (paper).

Psychiatrists with a philosophical bent seem to have gravitated toward phenomenology as a way of getting down to the basics of existence. Ludwig Binswanger, Karl Jaspers, and Medard Boss all turned to Husserl and Heidegger, as does Gordon Globus in this small, interestingly wrought, thoughtful, and somewhat provocative volume. Dr. Globus is a psychiatrist and a philosopher (he holds a dual professorship in both disciplines at the University of California, Irvine); he also did research on dreams earlier in his career. Therefore, his thinking ranges widely and penetratingly over the contributions of his predecessors in psychoanalysis and philosophy, and he culls from the leading edge of studies on brain function and cognitive science all that may be relevant to his thesis. His approach here is not clinical but epistemological. He makes it clear that his main concern is not what dreams mean but how an understanding of dreaming can shed light on the operation of waking consciousness and in so doing provide a "window on the human condition."

In the long opening chapter there is an attempt to lift dreams out of the secondhand aura that grew up about manifest content because of the greater emphasis placed on latent content. Manifest content was simply a mask behind which something more vital was to be found. Over the years, classical dream theory has endured, although not quite intact, despite criticism leveled at it almost from the beginning. Globus parts company with Freud on the basic issue of how dream images are related to waking experience. He characterizes Freud's view as one in which memory traces are "composited" into dream images. Despite rearrangements and superimpositions, they remain "mnemonic copies" of waking events. For Globus, this "compositional theory" seems implausible given the many ways in which dream images go beyond anything that could properly be attributed to a memory trace. Although he does not deny that dream images have some connection to waking life, he states that they seem more to be creatively formed *de novo*. Through this formative creativity dreamers find themselves in a "life-world" every bit as real as the waking world. Globus sees the connection between waking experience and dreaming not as the concrete representation of waking memory traces (regardless of the changes these images undergo in the course of condensation, displacement, etc.) but as occurring in a more abstract way. Here he uses the concept of "family resemblance," borrowed from Wittgenstein, according to which similarities occur that are not linked to any literal or specific characteristics in common but where one nevertheless senses that a relationship exists. Certain waking events are lifted out of their literal context and then, at a more abstract level, provide what Globus refers to as "abstract specifications," which become operative again during sleep and are fulfilled in the dream. The images thus generated are neither literal reworked memory traces nor translatable symbolic structures. Instead, they are a spontaneously generated "life-world," created *de novo* and

bearing only a "family resemblance" to the waking world. He contrasts this "formative creativity" with "syntactical creativity" (Freud's view), where the elements to be arranged creatively are already given as memory traces.

Having established that we create our dreaming world *de novo*, Globus's next task is to show that the same applies to our waking world. He goes about this by emphasizing the unreflective quality of dreaming existence and then postulating that the world experienced in this way is indiscernible from the waking world when we approach that world unreflectively. By this he seems to mean how we would experience that world were we to suspend our belief in the common-sense view of the world as existing out there and at the same time remove ourselves from our awareness of the sensory input that seems to make us experience it that way. We could then experience the world unreflectively and the two worlds, dreaming and wake, would be indiscernible. But is this so? Might it not be that if we were to disengage radically from sensory input, we would find ourselves lost in a chaotically hallucinatory world, as do subjects in a sensory deprivation experiment, instead of a waking "life-world" of our own creation?

Globus refers to his philosophical position as "monadological realism," implying that our individual "life-worlds" are constituted both awake and dreaming within autonomous monads. Drawing attention to the way the immune system possesses and is capable of evolving an infinite supply of antibodies to match any possible antigens, he likens the brain to such a system in its capacity to evolve, on a genetic basis (as in the case of Jung's archetypes) and as augmented by experience, an infinite supply of possible "life-worlds" to ensure reliable matches to external reality. Our individual "life-worlds" come into being through the transformations that occur at the interface between monad and the "energy sea" that surrounds us. We live out our lives awake and asleep alone in this monadic isolation from each other, each of us going about formatively creating our own "life-worlds." In contrast to direct realism, Globus's "monadological realism" holds that reality has to find its place within an autonomous "bubble of perception" in a windowless monad that engages external input only through matching filters.

Globus provides us with a new and thoughtful critique of classical dream theory on philosophical grounds. He succeeds in delivering the manifest content out from under the shadow of latent content and in doing so casts aside its secondhand status and allows the dream to shine forth as a creatively generated experience in its own right. Although this is incidental to the main thrust of the book, it is in itself an important contribution buttressing Jung's respect for manifest content and tempering Boss's immersion in the manifest at the expense of exploring connections to waking life.

Although I have difficulty in accepting Globus's admittedly counterintuitive account of our place in the world, I nevertheless found the voyage he took to reach his conclusions fascinating and replete with thoughtful critiques of all aspects of current thought that might have a bearing on our understanding of dreams. His scholarship and the range of his interests are impressive.

A word about the author's style. It is highly condensed. There are many references to Heideggerian terms that by their very nature are not easily definable. The task is made easier by frequent restatements of the author's line of reasoning, by a refreshingly informal tone at times, and by the frank and engaging way that he works on his own dreams.

MONTAGUE ULLMAN, M.D.  
 Ardsley, N.Y.

## EATING DISORDERS

*Eating Behavior in Eating Disorders*, edited by B. Timothy Walsh, M.D. Washington, D.C., American Psychiatric Press, 1988, 232 pp., \$22.95.

This volume contains 14 chapters that provide a wide range of observations in the growing field of laboratory and clinical investigations of eating behavior in both animals and man. The first five chapters provide reviews of laboratory findings of eating behavior, and the remaining nine report specific studies of clinical populations.

The review chapters are very up-to-date, with references to studies as recent as the last year and a half. Such is often not the case in books of this type, where there may be a long time between preparation of the initial manuscripts and publication of the final volume. It is gratifying, in this instance, to read chapters that are not already beginning to become obsolete.

The clinical chapters begin with a study of normal dieters, who display both normal and abnormal features in their eating patterns. Next is a study of taste, hunger, and satiety perceptions in patients with anorexia nervosa and bulimia. This study finds, interestingly, that taste preferences in such patients do not change even after apparent clinical recovery. The next two chapters examine gastric function in anorexia nervosa and bulimia and the phenomenon of "sensory-specific satiety" in patients with both normal and disordered eating.

The next four clinical chapters describe primarily studies of bulimic patients. These studies present useful observations of the nature of binge eating and vomiting episodes—phenomena that were formerly studied only through the retrospective accounts of bulimic patients but that now are being opened to laboratory scrutiny. These laboratory observations of bulimic behavior, together with measures of some of the biological changes that accompany such behavior, may yield exciting new insights into the syndrome of bulimia.

The final chapter reviews some of the methodological and theoretical aspects of laboratory studies of human eating behaviors. It points out that such studies in the laboratory setting may provide the control required to dissect the many factors contributing to the very complicated phenomenon of food intake and its control.

All in all, these chapters provide a comprehensive picture of laboratory studies of eating behavior. Not only does this book cover a wide range of investigations in this growing area of research, but it has managed to do so with very up-to-date presentations of the various fields involved. Whether readers are interested in normal eating, anorexia nervosa and bulimia nervosa, or obesity and dieting, they are bound to find many new and interesting observations in this book.

HARRISON G. POPE, JR., M.D.  
Belmont, Mass.

*Anorexia and Bulimia Nervosa: Practical Approaches*, edited by Derek Scott. New York, New York University Press, 1989, 214 pp., \$35.00.

Treatment of anorexia and bulimia using a multidisciplinary program is held to be the most effective treatment model at the present time. This includes specialized psy-

chotherapy, nursing services, occupational therapy, dietary counseling, rehabilitation counseling, self-help support groups, individual groups, and family therapy as indicated. The editor of this book is to be commended for his fine overview of psychological factors, systematic assessment, treatment planning, and program implementation. The discussion of psychodynamic factors focuses on the difficulties in separation and individuation and emphasizes that excessive emotional dependence on the family characterizes anorexia and bulimia nervosa in male and female patients, although Mr. Scott points out that a general lack of sexuality and aggression characterizes the male patient.

Individuals with anorexia and bulimia share in common a fear of fat and a desire for thinness. Although diagnostic questionnaires are helpful in the evaluation process, they do not relieve the clinician of performing a responsible and insightful interview. Questionnaires focus on and objectively measure the specific and unique attitudinal and behavioral features of the syndrome.

A variety of resources contribute to the treatment paradigm and help maximize social functioning and increase self-esteem. Chapters on self-help groups based on the Alcoholics Anonymous model, behavioral-therapy-based psychological approaches such as cognitive response prevention, and stimulus control are used to address the patient's irrational beliefs. A variety of psychotherapeutic approaches are presented, including Rogerian, psychoanalytic, feminist, and systemic family therapy. Anorexia and bulimia carry a 10% to 20% mortality rate; many of those who die of these illnesses committed suicide. Pharmacological intervention is considered helpful, but definitive studies regarding biological propensity and abnormalities in the CNS neurotransmitters are not available at this time.

*Anorexia and Bulimia Nervosa* correlates a wealth of current literature on the ideology and treatment of eating disorders. It is multiauthored and draws on the expertise of the efforts of many disciplines, reflected in the use of the treatment team and the current method of treatment of the disease. There is a concentration on anorexia; the chapters on bulimia are less detailed. It is well recognized that the anorexic state is a disorder predominately seen in female patients, but a brief discussion of the presentation in male patients is included, along with experience with young adolescent children.

The book is to be commended as a brief overview that emphasizes the multidisciplinary approach to treatment, which has been proven to be effective.

JUDITH SALLÉ YONGUE, M.D.  
Greenville, N.C.

## NEUROBEHAVIOR

*Epilepsy, Behaviour and Cognitive Function*, edited by Michael R. Trimble and Edward H. Reynolds. New York, Alan R. Liss, 1988, 214 pp., \$65.00.

For decades, epilepsy and madness have been tied together in the minds of the public and the professions. For most of the past century, epilepsy has been the concern of alienists; but as neurologists carved out their own discipline, they saw much epilepsy that appeared separate from mental illness. The separation seemed assured with the development of electroencephalography by Hans Berger in 1929. As the neuro-



logical perspectives of epilepsy were studied, however, psychiatrists kept epilepsy in the psychiatric camp by developing ideas of subclinical or larval epilepsy, or the behavioral syndromes of temporal lobe epilepsy.

One of the editors of this book, Michael Trimble, is a consulting psychiatrist at the Institute of Neurology and the National Hospital for Neurological Diseases at Queen Square in London. Trimble has sought to define the behavioral consequences of epilepsy and to encourage a rapprochement between the disciplines. He has written or edited *Epilepsy and Psychiatry* (1) and *What Is Epilepsy?* (2) (both with E.H. Reynolds), *Aspects of Epilepsy and Psychiatry* (3) (with T.G. Bolwig), and the textbooks *Neuropsychiatry* (4) and *Biological Psychiatry* (5). The present volume is in this tradition; it is the result of a symposium held in 1987 to discuss the cognitive and behavioral complications of poorly controlled epilepsy.

Twenty participants, mainly from the United Kingdom and France, discussed the difficulties inherent in assessing the effects of seizures on cognition and behavior and their impact on the education of children. The authors mainly summarize their own work. Little original material is presented; the inquisitive reader will have to go to original sources for useful data.

Aggressive outbursts in children with epilepsy are often ascribed to their seizure disorder. P.J. Thompson of Buckinghamshire, U.K., however, uses interesting case vignettes to illustrate the difficulties in assessing this association and argues that the association is not a feature of the disease.

Do epileptic patients experience mood disorders as a result of their disorder? Mary M. Robertson of London concludes from clinical experience that the rates of peri-ictal and interictal depression and even the risk of suicide are greater among poorly controlled epileptic patients than among the rest of the population. Mania and elation are rarely seen. Trimble emphasizes the direct effects of anticonvulsants on mood.

Do antiepileptic drugs affect cognition during treatment? Dennis B. Smith of Portland, Ore., summarizes collaborative antiepileptic drug trials of the Veterans Administration and concludes that there is no specific cognitive deficit associated with the use of any established antiepileptic drug. Christine A. Cull of Cheshire, U.K., and Trimble, however, present their own data, which revealed deficits associated with some anticonvulsants but not with others.

The editors include abstracts of informal discussions after each group of presentations. These helpfully elucidate some controversial issues. The articles have good citation lists, and there is a useful index.

At one point in one of the discussions, P.B.C. Fenwick of London asks, "Do you [E.H. Reynolds] feel that psychiatrists or neurologists are the people to treat epileptic patients?" In reply, Reynolds gives a lengthy statement arguing that "epilepsy does not belong exclusively to psychiatry or neurology but to physicians who take an active interest in it." This volume, and the others edited by Trimble and Reynolds, usefully encourage rapprochement between the disciplines.

Knowledgeable experts will be disappointed if they seek resolution of the thorny clinical problems discussed at the symposium. However, epileptologists faced with advising parents on the best strategy to maintain the education of an epileptic child and child psychiatrists faced with advising parents of children with behavior problems regarding the interaction among seizures, drugs, mood, and behavior will get some help. The volume is too terse and technical for medical students or residents in training.

## REFERENCES

1. Reynolds EH, Trimble MR (eds): *Epilepsy and Psychiatry*. London, Churchill Livingstone, 1981
2. Trimble MR, Reynolds EH: *What Is Epilepsy? The Clinical and Scientific Basis of Epilepsy*. Edinburgh, Churchill Livingstone, 1986
3. Trimble MR, Bolwig TG (eds): *Aspects of Epilepsy and Psychiatry*. New York, John Wiley & Sons, 1985
4. Trimble MR: *Neuropsychiatry*. New York, John Wiley & Sons, 1981
5. Trimble MR: *Biological Psychiatry*. New York, John Wiley & Sons, 1985

MAX FINK, M.D.  
Nissequogue, N.Y.

*Principles of Neurology*, 4th ed., by Raymond D. Adams, M.D., and Maurice Victor, M.D. New York, McGraw-Hill Information Services, 1989, 1,235 pp., \$65.00.

Single-volume presentations of complex and growing fields such as neurology or psychiatry are difficult. That *Principles of Neurology*, written by two respected neurological authorities, has demonstrated its competency in this endeavor is evidenced by the presentation of this fourth edition. *Principles of Neurology* has proved to be one of only two or three single-volume texts of neurology that have a confirmed usefulness for both the neurological specialist and the specialist in nonneurological fields. It has consistently proved to be an excellent reference source and is probably the most widely used text for Board examination preparation. Based on these accomplishments alone, *Principles of Neurology* has established itself as a lifetime reference source for many neurologists and psychiatrists.

This new edition maintains the format and the excellence of the previous editions. Much of the material is unchanged, but important additions have been made. For instance, there is an entire new chapter on the hypothalamus and neuroendocrine disorders, reflecting the important advances being made in hormonal aspects of nervous and mental symptoms. There are several entirely new sections, including one on the neurological manifestations of AIDS and another concerning Lyme disease. New discussions outline the use of botulinus toxin in the treatment of dystonia and review the genetic basis of the dystrophies. The book contains a sizable number of new, up-to-date references and a number of new illustrations, particularly reflecting the increased influence of magnetic resonance imaging on the field of neurology.

*Principles of Neurology*, 4th ed., is substantially larger than the third edition, is well written and documented, and will maintain the respected position of this text in the libraries of practitioners of nervous and mental diseases. For those looking for a single textbook on neurology, this volume is strongly recommended.

D. FRANK BENSON, M.D.  
Los Angeles, Calif.

*Pediatric Behavioural Neurology*, vol. 1: *Clinical Principles*, by Charles Njikiktjen. Amsterdam, Suyi Publicaties, 1988, 386 pp., 130 Dutch guilders.

This book is an important step in the process of conceptualizing and defining brain-behavior correlations in dis-

orders of childhood, analogous to the many behavioral neurology treatises available in the adult literature. The conceptualization of these disorders in neural terms is very important, and this book captures the essence of this model of thinking. As in the adult literature, the complexity of human behavior and the limited understanding of neural mechanisms of complex behavior make discussion of brain-behavior correlations particularly speculative for many disorders. The framing of these disorders in terms of neural mechanisms and in the context of brain development, however, represents an important approach, regardless of the accuracy of the specifics in some instances. In addition, the author integrates the psychological viewpoint of development rather well in the context of development and disorders of higher cortical function and behavior. This book's strengths are in 1) the conceptualization of developmental and behavioral disorders as disorders of evolving neural systems and 2) the breadth of this conceptualization. It also provides a practical perspective on the use of many common testing procedures. The book is not for readers looking for a thorough review of each topic, which can be found in conventional pediatric neurology textbooks, or a review of recent research developments. It is for the reader who wants to develop concepts of behavior in terms of neural systems for childhood disorders.

NANCY J. MINSHEW, M.D.  
Pittsburgh, Pa.

## MEDICAL PSYCHIATRY

**Handbook of Behavioral Medicine for Women**, edited by Elaine A. Blechman and Kelly D. Brownell. Oxford, Pergamon Press, 1989, 451 pp., \$75.00.

This book purports to "explain and give meaning to . . . behavior theory and women's health." Unfortunately, it falls short of its goals.

Psychiatrists and other physicians interested in women's health will note serious lacunae of medical information as well as misinformation, in my opinion. Unfortunately, female and male psychiatrists who are experts in the fields of women's health and behavior are not chapter authors; nor, I suspect, were they asked to critically review the manuscript.

In chapter one, "Infancy Through Childhood," Ronth and Anderson describe medical diagnoses, diagnostic techniques, and medical treatment through the well-meaning eyes of nonphysicians. The physician cannot help but be dismayed and put off by endless unexpectedly simplistic statements. In chapter two, "Puberty and Adolescence," for example, the authors state, "Biologically through the process of puberty, it is during adolescence that girls become women" (p. 12).

In the section on hyperemesis gravidarum, the authors of the chapter entitled "Disorders in Pregnancy" state, "Empirical research provides some support for the concept of immaturity (Harvey and Sherfey, 1954)." Further along, in discussing behavioral self-control training to help a woman control her hyperemesis, the authors state that she was referred "unfortunately reluctantly" by her obstetrician to a psychologist. She thus felt that the disorder was "in her head." The authors continue, "to improve the effectiveness of any behavioral intervention, it is useful to train the referring physicians in how to make referrals. The physician can point out that she/he is making a referral to a psychologist

who does not work with mentally disordered people but with psychologically healthy people who are undergoing unusual stress because of a medical disorder" (p. 105). As physicians many of us have learned that in fact gastric acid contents change during pregnancy and can lead to nausea and vomiting. I have found success in treating women with hyperemesis gravidarum by recommending very frequent small meals that include protein, fat, 1-2 tablespoons of scrambled eggs, a piece of cheese, carbohydrate, and a bit of apple pie.

Chapter nine, "Sexual Functioning," offers useful information about normal and abnormal functioning and particularly about side effects of medications that may interfere with sexual functioning.

In discussing osteoporosis (p. 51), a reference is cited "reporting positive gains in bone mineral of the radius midshaft." Most probably it should be the radius midshaft.

In chapter three, "Adulthood," beyond a number of grammatical errors and simplistic statements, the putdowns of physicians (p. 46) are clearly untrue and unnecessary. The authors recommend that behavioral clinicians "attain a clear assessment picture of symptoms and a careful health status because a woman presenting with depression and anxiety might benefit from appropriate behavioral treatment. Behavioral clinicians should be knowledgeable so patient's concerns can be understood and given honest, appropriate and reasonable responses"—perhaps implying that physicians do not.

Of the 61 contributing authors, four are physicians: one is a male neurologist, one is a female obstetrician, one is a male oncologist, and one is a male internist.

My notes of errors and omissions extended beyond four pages, excluding corrections to the text, through page 150.

Clearly, this book contains some useful information, but psychiatrists would do well to learn more about women's health and the related psychology of women by looking elsewhere.

LEAH J. DICKSTEIN, M.D.  
Louisville, Ky.

**The Medical Evaluation of Psychiatric Patients**, by Randolph B. Schiffer, M.D., Robert F. Klein, M.D., and Roger C. Sider, M.D. New York, Plenum, 1988, 237 pp., \$35.00.

This is an outstanding book that provides a practical and useful summary of those neurological and medical illnesses which are often clinically indistinct from major psychiatric disorders. Both consultation psychiatrists and psychiatrists practicing in a general hospital setting should find this a particularly valuable addition to their medical libraries. This book complements the more comprehensive *Principles of Medical Psychiatry*, edited by Alan Stoudemire and Barry Fogel (1). In contrast to the latter, which contained 33 chapters and more than 700 pages, *The Medical Evaluation of Psychiatric Patients* contains nine chapters and fewer than 250 pages of text. It is not intended to be comprehensive but focuses instead on providing useful information that may be of direct use to psychiatrists in their clinical practices.

The authors organized their book in a logical framework. They begin with two chapters focusing on why psychiatrists are reluctant to perform a physical examination. They articulate an interesting historical review of how modern psychiatry evolved and how in the early 1970s psychiatry in the United States distanced itself from the rest of medicine by eliminating the internship requirement. The authors also

summarize why psychiatrists may object to or avoid performing a physical assessment of their patients. This chapter was an interesting discourse and led to the "not-so-modest proposal" of the authors: psychiatrists, to understand their patients as complete persons, need to complete a physical assessment in addition to a psychiatric assessment. The authors contend that such a balance between psychological and physical assessment leads to higher quality care and a more complete understanding of patients. Chapter two addresses the general issue of the relative prevalence and incidence of physical illness among psychiatric patients. The authors discuss medical morbidity and mortality studies of psychiatric patients and summarize general population studies of psychiatric disease and mortality. They conclude by emphasizing the responsibility of psychiatrists to recognize physical illness in their patients. In other words, chapter one provides a philosophical framework and chapter two a more objective analysis of the reasons why a physical assessment should be an integral part of psychiatric practice in the 1990s.

The next two chapters focus on the neurological examination and the general physical examination. Both chapters are clearly and concisely written. The authors emphasize that they are providing a general outline of the neurological and physical examination for psychiatrists. They provide specific examples of how to conduct particular components of the neurological examination and the physical examination. The chapters are written in such a style that readers feel that the authors are conversing directly with them in providing a curbside consultation, just as one would receive during teaching rounds.

The remaining five chapters focus on major psychiatric syndromes (depression, mania, anxiety, paranoid psychosis, and nonparanoid psychosis) that may be caused by drugs, toxins, or medical and neurological diseases. These chapters contain a number of helpful tables, mnemonics, case examples, and figures. For instance, the authors provide wonderful summaries of the laboratory approach to suspected conditions and give brief reviews of pathophysiological processes that may produce psychiatric syndromes. The authors also provide normal ranges for selected tests. Each chapter begins with *DSM-III-R* and *ICD-9* diagnoses that are associated with the particular syndrome. For each medical disorder associated with the syndrome they discuss general medical findings, laboratory and imaging findings, and neurological findings. Whenever appropriate, they emphasize relevant aspects of the clinical history, mental status examination, drug-drug interactions, and patient demographic characteristics that may be related to the disorder.

The major strength of this book is in the clear, precise prose and the wealth of material that is provided in such an abbreviated yet complete fashion. The writing style is pleasing. The language is direct, and the writers use declarative statements to make their points without equivocation. All of the chapters are well referenced, including articles published as recently as 1987. The book contains a helpful index and well-organized chapters.

My only criticism of the book is in the authors' distinction between paranoid and nonparanoid psychosis. For instance, they include in the nonparanoid psychosis chapter several schizophrenic disorder subtypes, amphetamine delusional disorder, cannabis delusional disorder, cocaine delusional disorder, and other conditions as examples of those disorders which are representative of this syndrome. Many clinicians would contend that patients with these disorders also frequently manifest paranoid symptoms. Instead of dividing psychosis into two chapters, it would seem logical to have

included only one chapter and not try to distinguish between paranoid and nonparanoid characteristics.

In summary, this is a very readable and useful book that should be widely read by psychiatrists interested in the practice of "medical psychiatry." I recommend it most highly and find that I have already turned to it on several occasions to obtain answers to questions from residents concerning psychiatric evaluations.

#### REFERENCE

1. Stoudemire A, Fogel BS: Principles of Medical Psychiatry. Orlando, Fla, Grune & Stratton, 1987

ROBERT E. HALES, M.D.  
Mill Valley, Calif.

**Neurobehavioral Disorders: A Clinical Approach, 2nd ed.,** by Richard L. Strub and F. William Black. Philadelphia, F.A. Davis Co., 1988, 507 pp., \$53.00.

In this work the authors have revised and expanded their 1981 book, *Organic Brain Syndromes: An Introduction to Neurobehavioral Disorders*. The basic organization of the earlier book has been retained, but individual chapters have been expanded and updated, and the bibliographies at the conclusion of each chapter have been substantially increased.

The reader is presented with an overview of much of our current knowledge concerning brain-behavior connections. The chapters are organized within four major topic sections: Anatomy and Clinical Evaluation, Major Neurobehavioral Syndromes, Neurobehavioral Syndromes of Specific Etiologies, and Borderline Neurobehavioral Disorders. The authors present each chapter much as a clinician might think about a clinical problem, moving from case vignettes through history and mental status examinations to medical and laboratory diagnosis and management. This is generally an effective organization for the chapters, especially for those clinicians who might wish to review a given neurobehavioral topic.

Section one, which presents the neuroanatomy of behavior and a thorough discussion of mental status evaluations, deserves particular praise. A neuroanatomical hierarchy by which to understand behavior is well presented, including discussion of neurotransmitter and projection systems. The diagrams are quite understandable, especially of brainstem structures. Both bedside mental status examination techniques and more sophisticated neuropsychological testing are clearly discussed. Even the most experienced interviewer will pick up a tip or two from these chapters. This first section may represent the apogee of the book and deserves familiarization by all psychiatrists.

The subsequent major sections of the book discuss clinical aspects of neurobehavioral syndromes. These chapters include such topics as an approach to the dementias, behavioral disorders seen with focal brain lesions, trauma, toxins, and infections. Readers not particularly familiar with behavioral neurology will find these chapters a good introduction. The succinct descriptions of agnosias, aprosodias, aphasias, and apraxias are especially worthwhile. The sheer breadth of material covered in these chapters becomes their limitation, however. "Infections of the Central Nervous System," for example, are covered within the space of 18 pages. No one

can discuss this issue in that space and present something of more than introductory value.

With the limitations noted, the book remains highly recommended for psychiatrists in training or for psychiatrists who wish to brush up on neurobehavioral disorders. It also provides reasonable referenced access to the wider research literature.

R.B. SCHIFFER, M.D.  
Rochester, N.Y.

**Psychosomatic Medicine and Contemporary Psychoanalysis**, by Graeme J. Taylor, M.B., Ch.B. Madison, Conn., International Universities Press, 1987, 391 pp., \$37.50.

This useful and scholarly book was started while the author was on sabbatical at the University of California, Los Angeles. I had an opportunity to meet him during the time he was there. Now I am able to review his book. I believe that it is a historically important volume. It is extremely well researched and well written. It is also a much larger work than the title suggests because it includes all of medicine in its scope. Therefore, if one accepts that all of medicine is "psychosomatic" and that contemporary psychoanalysis includes the view of human relationships as dynamic systems affecting the mind, it is a treatise on medicine and psychoanalysis. It is also clear that this book is not written only for consultation-liaison psychiatrists but is addressed to psychobiologists, psychophysicists, philosophers of medicine—in short, the Renaissance men and women in all fields of science.

In the early chapters, the author attempts to bring together psychobiology and psychoanalysis. These fields, closely related to each other historically, have drifted apart in recent years. The author argues that human disease encompasses both pathways. As John Nemiah states in the foreword: "Dr. Taylor's skillful interweaving of threads from many disciplines should make it increasingly obvious to all physicians that pathophysiology of the gut and body is inseparable from human experience and relationships."

In its final chapters, which may be more understandable to psychoanalysts who are familiar with object relations theory, the author attempts to relate the role of human relationships in the regulation or dysregulation of physiological function, a holistic view that encompasses the work of Engel, Weiner, Hofer, Nemiah, and Sifneos as well as the object relations school of psychoanalysis. Thus, it becomes a very special book for psychoanalysts.

For the consultation-liaison psychiatrist, the book fills a very real need. It has been generally recognized that the best consultation-liaison psychiatrists are not necessarily those who have had previous training in internal medicine or family practice but are often those who are the most well-rounded psychiatrists, whatever their previous training and experience. Consultation-liaison psychiatrists who are interested in psychoanalysis and psychodynamics bring to their work a deeper perspective and understanding of the importance of human relationships and their contribution to clinical medicine.

This is not a handbook; it is a book for reflection and study. It is not a text; it is a treatise. It is clearly not for everyone. However, it represents a scholarly effort to restore psychoanalysis to its rightful place in psychosomatic medicine by reviewing

the very relevant recent advances in psychoanalytic knowledge and theory.

ROBERT O. PASNAU, M.D.  
Los Angeles, Calif.

**Neurobehavioral Recovery From Head Injury**, edited by Harvey S. Levin, Jordan Grafman, and Howard M. Eisenberg. New York, Oxford University Press, 1987, 415 pp., \$35.00.

Whether your perspective is from clinical care, research, or the desire for more knowledge about the psychological and behavioral consequences of traumatic brain injury, this is a "must read" book. To meet the needs of readers who are at all levels of knowledge about cognitive and psychiatric outcomes, the book must focus at times on the forest and at other times uses a microscope on the tree bark. It accomplishes both tasks well. The breadth of the text is evidenced by its division into eight sections and 28 chapters. The first section addresses methodological issues in the use of clinico-pathological correlations in outcome studies of head injury. In this section, Drs. Eisenberg and Weiner provide a detailed description of the Glasgow Coma Scale and examine those variables which predict the final outcome of patients with head injury. Dr. Langfitt et al. provide case descriptions that illustrate the utility of and problems presented by different imaging techniques, and Drs. Grafman and Salazar describe clinical differences between open and closed head injuries and their influence on cognitive and behavioral outcomes.

The second section is devoted to design, management, and analysis of neurobehavioral outcome studies. Dr. Brooks examines the problems of longitudinal studies, such as maintaining an adequate follow-up. Drs. Dikmen and Temkin examine problems in the determination of the effects of head injury and recovery in behavioral research, and Drs. Strauss and Allred provide a thoughtful evaluation of statistical problems in data analysis.

The third section is devoted to neuropsychological assessment of patients with head injury. After an introduction by Dr. Benton, Dr. Lezak revises those neuropsychological measures which are relevant to patients with head injury, Dr. Newcombe considers problems in contemporary practice and delineates directions for future research, and Drs. Diller and Ben-Yishay examine measurements of improvement in the functioning of patients undergoing rehabilitation. Dr. Stuss makes the point that frontal lobe injury (a frequent finding in patients with head injury) leading to changes in ability to sequence, generate drive, and assess the self might explain some of the cognitive problems shown by these patients. Finally, Dr. Oscar-Berman examines experimental approaches to the study of cognition in patients with head injury.

The fourth section is devoted to the outcome of patients with head injury from neurological (Dr. Alexander) and neurosurgical (Dr. Marshall) perspectives, with emphasis on neuropathological findings.

The fifth section deals with psychiatric sequelae of head injury. After an introductory chapter by Dr. Prigatano, Drs. Grant and Alves examine those DSM-III-based psychiatric disorders which are most frequently found in patients with head injury. Finally, Dr. Levin et al. examine such issues as the postconcussional syndrome in patients with minor head injury.

The sixth section is devoted to head injuries in children,



and Dr. Fletcher et al. consider the importance of age as a variable in the recovery from head injury.

The seventh section (an investigator's delight) is devoted to memory problems. Dr. Baddeley et al. examine short- and long-term memory deficits in patients with head injury, as well as deficits in episodic and procedural memories. Dr. Corkin et al. examine the main aspects of retrograde amnesia and posttraumatic amnesia, as well as their (lack of) relationship. Dr. Crovitz provides useful examples of different techniques to investigate posttraumatic and retrograde amnesia, and Dr. Tulving provides a theoretical framework for the study of memory problems in patients with head injury.

Section eight, another excellent section, deals with attentional problems after head injury. Dr. Gronwall's review of attentional deficits in patients with head injury is followed by Dr. Buchtel's chapter on vigilance tasks to measure attention and Dr. Papanicolaou's chapter on the importance of evoked potentials in the measurement of attentional deficits. Finally, Dr. Posner provides a theoretical framework for the study of attentional deficits in patients with head injury, and Drs. Van Zomeren and Brouwer summarize their own findings as well as potential discrepancies with other reports.

Although the book is multiauthored, it has been tightly edited and, except for very minor repetitions (the Stroop test is described in two different chapters), it lacks the usual problems of multiauthored books. Moreover, since the chapters were written by some of the most prominent investigators in their areas, the book has a consistently high quality. There are very few books that deal with the behavioral and psychological as well as cognitive consequences of brain injury. This may be one tree in a small forest, but all trees should stand this tall.

ROBERT G. ROBINSON, M.D.  
SERGIO E. STARKSTEIN, M.D.  
Baltimore, Md.

## CHILDREN AND ADOLESCENTS

**Professional Responsibilities in Protecting Children: A Public Health Approach to Child Sexual Abuse**, edited by Ann Maney and Susan Wells. New York, Praeger, 1988, 222 pp., \$39.95.

This is a brave, harsh, well-researched, well-reasoned, and well-written book, but it will probably be read only by those who least need its priceless treasures because they already work with victims and perpetrators of child sexual abuse.

The 20 contributors from the fields of medicine, law, psychology, and nursing give "approximate" answers to the following basic questions: 1) Are most incidents of child sexual maltreatment now officially reported? 2) Does reporting in fact result in case identification? 3) Do the benefits to the child from case identification outweigh the psychic and social costs all around?

For question number one, the answer is a resounding no. For every official substantiated report of sexual maltreatment involving physical contact in the 1979 National Incidence Survey data, 14–52 incidents were unreported. For every substantiated report of sexual maltreatment involving physical contact that was active with a major investigation agency other than child protective agencies, 8–31 incidents were unreported. Reporting per capita (not per child) doubles in

those areas where comprehensive treatment programs are made available.

To the second question, the answer is as frustrating and discouraging as the story of Pandora's box and the leak in the dike story. Many states have a subjective, inconsistent concept of triage: the judgment is almost always left up to the assigned caseworker. To add to the further muddling of data collection, the National Incidence Survey not only limited the total sample of child protective services to substantiated cases but also dropped substantiated cases that did not involve physical contact (53%). This subset of sexual maltreatment cases might be expected to involve siblings at risk to an unusual degree for molestation as well as offenses in which protracted harassment or escalating deviance is at issue. (Some of these might have been directed into the emotional abuse category.)

As for the question of costs and benefits, these are virtually impossible to assess. The size of the average child protective service caseload has increased beyond the standard for good practice. The authors also report that new technologies to alleviate the stress of testifying and provisions for closing courtrooms are seldom used because of "judicial and practical concerns."

In the midst of the felt eddies of Maeder's attack on the helping professions (1), chapter three, "Cultural Obstacles to the Labeling of Abuse by Professionals," should cause us to pause, stop all the rhetoric, and act. In Kim's 1985 study of two metropolitan areas, less than half of child abuse was reported. Almost 70% of the physician sample had never reported any suspected cases. Finkelhor's 1984 Boston study of professionals from various disciplines revealed that approximately 36% failed to report sexual abuse cases; mental health and criminal justice professionals failed to report suspected cases most often. These statistics became worse in cases where the child retracted an allegation of abuse. More than half of the psychiatrists and a third of the professionals from other disciplines chose not to refer such cases because they tended to believe that allegations of incest are fantasies. In fact, there is evidence (2) suggesting that fewer than 5% of children's reports of sexual abuse are falsified. The fact that many professionals neglected to urge the collection of more physical evidence and instead opted for a psychological evaluation of the suspected victim is astounding and reveals an ignorance of the dynamics of the family situation that may coerce a child into a retraction.

Abby Cohen's chapter, "Sexual Abuse in Childcare: A Special Case in Regulation and Legislation," is deserving of special mention because it is a very sober and well-balanced discourse on the aftershocks of the facts revealed in this book. Cohen states, "Although it is important to recognize that abuse can occur outside the family, it appears that society has chosen to overemphasize out-of-home abuse because of its inability to deal adequately with the more discomforting issue of intrafamilial abuse." The 20 suggestions concerning licensing in child care and Cohen's 10 bits of advice to parents about choice of child care are comprehensive, enforceable, practical, and show a great deal of sensitivity and common sense.

If you happen to have only 15 minutes that you can allot to reading this book, go directly to the last two chapters by Susan Wells. Unless you have the sensitivity of a cucumber or the vertebrae of the jellyfish, your medical practice will never be the same again.

## REFERENCES

1. Maeder T: The wounded healers. *Atlantic Monthly*, Jan 1989, pp 37-47
2. Chang A, Oglesby AC, Wallace HM, et al: Child abuse and neglect: physicians' knowledge, attitudes, and experiences. *Am J Public Health* 1976; 66:1199-1201

TRUCE T. ORDONA, M.D.  
Davenport, Iowa

*Juvenile Homicide*, edited by Elissa P. Benedek, M.D., and Dewey G. Cornell, Ph.D. Washington, D.C., American Psychiatric Press, 1989, 247 pp., \$24.95.

Just as I was about to write this review, I read about a 14-year-old boy who had killed his 12-year-old girlfriend in the context of an argument about whether she should have had an abortion. Although not all juvenile homicide is quite this tragic or hopeless, it does seem to have all the elements of homicides perpetrated by adults, in addition to the dimension of acts occurring in the midst of a developmental stage. This edited book brings out the diversity in juvenile killings and what those of us who work in this area have realized for some time: the procedures for dealing with these juveniles have moved ever closer to the adult criminal process.

Several of the chapters were presented initially at an annual meeting of APA at a panel organized by Dr. Benedek (at which I was a participant). I think that the papers presented at that meeting and the chapters in the present volume are good. Five of the nine chapters of this book are the product of work done at the Center for Forensic Psychiatry at Ann Arbor, where Dr. Benedek and some of her co-workers had an opportunity to study 72 youths referred during 1977-1985. They point out that their sample is not to be taken as representative of all adolescents who commit homicide, even in Michigan. The group was only a small percentage of adolescents who committed homicide in Michigan during that period. The authors' clinical experience led them to conclude that sample comparisons between such youths and other delinquent groups would be of limited value and not lead to useful generalizations (p. 40).

In a later chapter, however, Dr. Benedek and her group attempt to compare the 72 youngsters charged with homicide with 35 adolescents charged with larceny (car theft or breaking and entering) who were referred to their center for evaluation. Immediate problems are evident in the attempts to carry out such a comparison. Thirty-three (46%) of the 72 adolescents charged with homicide but only nine (26%) of the 35 charged with larceny were nonwhite. Why this was so and whether it casts doubt on the validity of the comparisons could be asked. Fewer of the adolescents in the homicide group than in the control group had any history of previous mental health treatment. However, the homicide group was also younger; 13 (18%) were 15 years old or younger, compared with only one subject (3%) in the larceny group. Similarly, 31 (43%) of the youngsters in the homicide group had no history of previous arrests, compared with seven (20%) of the larceny group. Whether these findings were due to the homicide sample being younger or perhaps coming from a different geographic area of Michigan is not known.

In developing a typology, the authors try a tripartite division of the homicide cases: 1) those in which the question of psychosis arises, 2) homicides committed during another

crime, and 3) conflict-related homicides. The case example used to illustrate these divisions are often left tantalizingly short for those who would like more explanation. The typology begins to go into the problem of classifying homicidal adolescents but is unsatisfying. The first and third categories are clinical classifications that, in turn, overlap. Although the problem of accurate diagnosis is essential to differentiate malingering from a psychosis, we are left with those adolescents caught up in conflicts related to the perpetration of a homicide. Also, the category of conflict-related homicides is defined in terms of the perpetrator's interpersonal conflict with the victim. There are many other types of conflict that can also give rise to a homicide, such as intrapsychic conflict or conflict with one's broader environment. The two examples given—murder of an abusive father and a 15-year-old boy charged with killing a 14-year-old girl—do not satisfy the many possibilities. Simply using a descriptive diagnostic framework of the *DSM* edition operating at the time would have given more fruitful information.

The middle category—homicides committed during another crime such as robbery, burglary, or rape—is actually a sociological or legal classification. Although that method of classification is valid for its purposes, such as sorting crime data, it still leaves many questions unanswered about the clinical status of a juvenile group and the recognition of differences among the individuals in it. For example, a youth who turns and blindly shoots while escaping from a grocery store holdup might be quite different from a youth who kills a victim in the course of a rape.

The different authors approach the problem of juvenile homicide from their own points of interest. Spencer Eth writes about adolescents who witness homicides. Gregory B. Leong discusses some of the clinicolegal issues in examining cases from his experiences in the Los Angeles County Superior Court. It is a good overview of the many issues, comparable to those seen in adult courts, that are now being raised in juvenile proceedings. Competency to waive *Miranda* warnings is even more complicated with juveniles than it is with adults because of the age of the person waiving and judicial confusion over what constitutes a competent waiver at younger ages.

W. Lawrence Fitch of the Institute of Law, Psychiatry, and Public Policy at the University of Virginia gives a scholarly legal analysis of the problems of competency for trial and responsibility in juvenile court. He reviews the vast changes that followed the *Gault* decision by the United States Supreme Court in 1967, which gives certain procedural protection to juveniles, such as written notice of charges, right to counsel, privilege against self-incrimination, and the right to confront and cross-examine witnesses. Although it now seems obvious, it did not occur to many in 1967 that this landmark case would actually be the beginning of a shift from an emphasis on the primary purpose of the juvenile system to rehabilitate. The result has been increasing criminalization, with accompanying rights for juveniles and little actual progress in rehabilitative efforts. As a result, we have witnessed the shift to discussions of the insanity defense with juveniles, certification of juveniles to adult courts, and capital punishment of juvenile cases before the Supreme Court. As Richard J. Bonnie of the University of Virginia Law School writes, this shift reflects the current legal ambivalence in dealing with individuals under the age of 18 who perpetrate a homicide.

CARL P. MALMQUIST, M.D.  
Minneapolis, Minn.

*Reprints of Book Forum reviews are not available.*

### Use of Extremely Low Doses of Fluphenazine Decanoate

SIR: There has been considerable interest in low-dose neuroleptic treatment, particularly in the use of low-dose fluphenazine decanoate (1–5). Kane et al. (1) reported doses as low as 1.25–5 mg every 2 weeks; Marder et al. (2, 4), 5 mg every 2 weeks; and Hogarty et al. (5), a mean  $\pm$ SD of  $3.82 \pm 2.1$  mg every 2 weeks. I would like to report a case in which the patient apparently responded to a dose of 0.5 mg (0.02 cc) of fluphenazine decanoate every 3 weeks.

Ms. A is a 50-year-old divorced mother of four children. She has an 11th-grade education and a minimal work history. She lives in a small house with her mother, her sister, and her sister's boyfriend.

Ms. A had barely managed as a single parent until 1970, when she decompensated following a physical assault by a boyfriend. She was isolated, seclusive, and delusional—with delusions about cancer, her uterus, surgery secretly performed on her, insects in her head—for most of the next 13½ years. During this period she had intermittent outpatient psychiatric treatment characterized by poor compliance and poor follow-up. Functionally, she became another child in her mother's home.

Ms. A's first psychiatric admission occurred in 1982 after her delusions and agitation rendered her unmanageable. Her verbal output at admission was described as unintelligible gibberish. She was discharged on a regimen of haloperidol, 10 mg b.i.d., but was rehospitalized 4 months later following an assault on her mother. She was described as delusional, agitated, paranoid, and demonstrating disordered thinking.

Ms. A was followed as an outpatient for the next couple of years, during which time she took thioridazine, 150–800 mg/day, with poor to fair results. Her compliance with this regimen was consistently problematic. She was then started on fluphenazine decanoate, 25 mg every 2 weeks, and took this dose for 7 months. The dose was gradually tapered to 0.5 mg every 3 weeks over the next 22 months without any signs of a thought disorder. During this period Ms. A was seen by a registered nurse every 3 weeks, a support worker once a week, and a psychiatrist every 8–12 weeks. This pattern of service remained constant throughout all subsequent medication changes.

In the spring of 1988 the fluphenazine decanoate was discontinued. One month later Ms. A complained of restlessness, anxiety, impaired sleep, and increasing confusion. The fluphenazine decanoate was restarted at 0.5 mg every 3 weeks and she returned to stable functioning. She took this dose for 1 year, and the medication was then again discontinued. Eight weeks later Ms. A began to decompensate; she was rehospitalized 12 weeks after the neuroleptic had been discontinued. She presented as confused, intermittently mute, and anxious; she demonstrated disordered thinking, thought blocking, and delusions when she did talk. She was restarted on fluphenazine hydrochloride,

5 mg/day, and was discharged after 1 week. Ms. A is now being treated as an outpatient and is taking progressively decreasing doses of fluphenazine decanoate, with the goal of returning to the dose of 0.5 mg every 3 weeks.

Although this naturalistic *abab* design, and the maintenance of constant services whether or not medication is being administered, decrease the likelihood of a placebo response, the possibility of such a response is certainly not eliminated. To treat Ms. A with placebo without informed consent would be clearly unethical; to do so with her consent to blind administration of placebo versus fluphenazine would not be possible, because Ms. A fears further decompensation if she does not take medication and will not agree to such a course.

While studies of low-dose fluphenazine decanoate therapy have indicated that the modal neuroleptic-responsive patient can be maintained on a dose of 5 mg every 2 weeks (1–5), this case should underscore the fact that with close clinical monitoring, a gradual, progressive decrease in dosage can result in efficacious treatment of some patients with extremely low doses of fluphenazine decanoate.

### REFERENCES

1. Kane JM, Rifkin A, Woerner M, et al: Low-dose neuroleptic treatment of outpatient schizophrenics. *Arch Gen Psychiatry* 1983; 40:893–896
2. Marder SR, Van Patten T, Mintz J, et al: Costs and benefits of two doses of fluphenazine. *Arch Gen Psychiatry* 1984; 41: 1025–1029
3. Kane JM, Woerner M, Sarantakos S: Depot neuroleptics: a comparative review of standard, intermediate, and low-dose regimens. *J Clin Psychiatry* 1986; 47:5(suppl):30–33
4. Marder SR, Van Patten T, Mintz J, et al: Low- and conventional-dose maintenance therapy with fluphenazine decanoate. *Arch Gen Psychiatry* 1987; 44:518–521
5. Hogarty GE, McEvoy JP, Muntz M, et al: Dose of fluphenazine, familial expressed emotion, and outcome in schizophrenia. *Arch Gen Psychiatry* 1988; 45:797–805

JEFFREY GELLER, M.D., M.P.H.  
Worcester, Mass.

### Psychoactive Abuse Potential of Robitussin-DM

SIR: The following case illustrates the continuing abuse potential of dextromethorphan, which is the antitussive component of Robitussin-DM.

Mr. A, a 22-year-old army private, arrived at an army hospital emergency room complaining of severe dysphoria due to failing an army training examination and acute marital discord. He attributed his immediate problems to daily consumption of 20–22 oz of Robitussin-DM (5–5½ regular-size bottles).

The patient related a history of polysubstance abuse starting at age 15. At age 16, on the suggestion of a drug-

abusing acquaintance, he drank a 4-oz bottle of Robitussin-DM. He described his mind-altering experience: "The high was 10 times greater than marijuana. It numbed me and solved my stress." Mr. A felt bad when he was not taking the drug and became strongly addicted mentally. He typically would consume his first bottle in the morning, waiting about 45 minutes for the effect, then drink an additional bottle about every 4 hours for a "16-hour buzz that would set me for the whole day." His use of dextromethorphan satisfied the *DSM-III-R* criteria for psychoactive substance dependence. A few times he had sought help from professionals, including a clergyman, a youth director, and a psychologist. However, he felt that they did not take him seriously because they did not understand the effects of the medication. He once told his pharmacist about the problem, but the pharmacist apparently declared, "It is impossible to get high on Robitussin."

Dextromethorphan hydrobromide is the antitussive ingredient used in at least 60 over-the-counter preparations. It is a morphinan analogue, and its parent compound is morphine. Manifestations of acute toxicity include nausea, vomiting, drowsiness, dizziness, urinary retention, urticaria, stupor, toxic psychosis, insomnia, hallucinations, hysteria, and coma. Mr. A reported difficulty sleeping (he slept only 4 hours per night); urinating up to 20–25 times a day; severe abdominal gas, pressure, belching, and occasional vomiting; slow, slurred speech; and difficulty focusing his vision. He also reported ataxia, which precluded marching: "My legs were stepping 6 feet out in front of me."

Real abuse is associated with this agent, and it is known in the popular culture as a drug with the potential for abuse (1). It was available in tablet form (Romilar) about 30 years ago and was subsequently withdrawn from the over-the-counter market because of an abrupt upswing of sales and abuse. It was then remarketed in a mixture of excipient syrups and preparations that might discourage intentional intoxication (1). However, a "high" is produced with the consumption of only one 4-oz bottle (2). Abuse of dextromorphan was also described in Europe in 1968 (3) and 1972 (4), and it was labeled as an "escape drug." There has been no recent publicity concerning its potential for abuse.

We hope that health care providers and school guidance counselors will become more familiar with this over-the-counter substance and treat the severity of the psychological dependence on this drug with the same seriousness that they do that of other psychoactive substances.

#### REFERENCES

1. Shulgin AT: Drugs of abuse in the future. *Clin Toxicol* 1975; 8:405–456
2. Mansfield C, Piazza NJ: Lesser-known uncontrolled psychoactive substances and their effects. *Counseling and Development* 1986; 65(2):104
3. Bornstein S, Czermak M, Postel J: [Apropos of a case of voluntary medicinal intoxication with dextromethorphan hydrobromide]. *Ann Med Psychol (Paris)* 1968; 1:447–451 (French)
4. Kielholz P, Ladewig D: Drug dependence in the young. *Foreign Psychiatry* 1972; 1(1):64–76

JOHN HELFER, M.D.  
OKSUK MARY KIM, M.D.  
Augusta, Ga.

#### Psychological Distress Related to Sexual Abuse in a Patient Undergoing Hemodialysis

SIR: Several recent reports have documented high prevalence rates of sexual abuse reported by psychiatric inpatients (1) and outpatients (2). Although sexual abuse during childhood has been linked to chronic pelvic pain (3), we know of no reports specifically addressing sexual abuse in the histories of psychiatric patients seen in the consultation-liaison setting. We report here a case in which childhood sexual abuse contributed to psychological distress in a patient undergoing hemodialysis.

Ms. A was a 38-year-old woman who was referred by the medical service for her third psychiatric consultation in 8 months because of her "notorious noncompliance" with chronic hemodialysis, which included missing scheduled dialyses and prematurely terminating dialysis once it had gotten underway. Referrals for outpatient psychiatric treatment made during previous consultations had not been accepted by the patient.

During this admission, Ms. A described having been repeatedly raped and sexually abused by her stepfather from age 5 to 10, typically several times a week. Although she initially described the abuse with a bland affect, she became quite sad and tearful when asked if hemodialysis reminded her of being abused. She described having memories of the abuse during her dialysis treatments, which would often become so painful that she would have to stop the treatment or avoid treatments altogether. She felt that dialysis, like sexual abuse, meant losing control over her body; it seemed like a repetitive experience of being physically intruded upon by caretakers.

Following what appeared to be an emotionally cathartic experience, Ms. A began, and continues in, outpatient psychotherapy. She has not required medical admission in the subsequent 5 months, compared to four medical admissions precipitated by noncompliance in the previous 8 months.

Routine inquiry about a history of sexual abuse and/or rape should now be considered part of a comprehensive psychiatric evaluation (3). Noncompliance with a hemodialysis regimen is multifactorial (4); further investigation would be necessary before concluding that past sexual abuse is a significant component of hemodialysis noncompliance in general. However, we suggest that since repeated intrusive medical or surgical procedures mimic certain aspects of sexual abuse, consulting psychiatrists should be especially alert to the possibility of childhood sexual abuse when patients are referred for noncompliance with such procedures.

Avoidance of situations that remind one of past trauma is characteristic of posttraumatic stress disorder as described in *DSM-III-R*. Reframing the patient's noncompliance behavior as such may help medical and nursing staff avoid adopting harsh, controlling stances ("You have to *have* this done") that may remind the patient of abuse.

We welcome further study of this topic.

#### REFERENCES

1. Bryer JB, Nelson BA, Miller JB, et al: Childhood sexual and physical abuse as factors in adult psychiatric illness. *Am J Psychiatry* 1987; 144:1426–1430
2. Jacobson A: Physical and sexual assault histories among psychiatric outpatients. *Am J Psychiatry* 1989; 146:755–758



3. Walker E, Katon W, Harrop-Griffiths J, et al: Relationship of chronic pelvic pain to psychiatric diagnoses and childhood sexual abuse. *Am J Psychiatry* 1988; 145:75-80
4. Gonsalves-Ebrahim L, Sterin G, Gullledge AD, et al: Noncompliance in younger adults on hemodialysis. *Psychosomatics* 1987; 28:34-41

JOHN KRAWCZYK, M.D.  
VALERIE D. RASKIN, M.D.  
*Chicago, Ill.*

### Control of Bed-Wetting With Benztropine

SIR: Bed-wetting is a humiliating experience frequently encountered by chronic, treatment-resistant schizophrenic patients. Most institutions use behavioral methods—such as restricting water intake, getting patients to urinate before going to bed, and/or awakening them during the night to urinate (1)—to control bed-wetting. These measures are helpful but often inadequate. Small doses of imipramine and propantheline bromide have been used in the treatment of children with enuresis and of geriatric patients. The success of these compounds is most likely due to their intrinsic anticholinergic activity.

We observed that clozapine, an investigational antipsychotic drug with marked anticholinergic activity (2), stopped bed-wetting in two schizophrenic patients. This observation motivated us to look at benztropine, a potent, long-acting anticholinergic compound, as a potential treatment for nocturnal enuresis in this patient population.

Six patients who had been wetting their beds every night for several weeks were given benztropine, 4 mg p.o. at 8:00 p.m. All of these patients were adult men (mean age=38.5 years; range=32-45) with chronic schizophrenia who had been hospitalized for several months and were taking a variety of medications, including neuroleptics, lithium, and benzodiazepines. The usual behavioral methods for controlling bed-wetting had been tried and had been unsuccessful. Within 4-5 days of starting benztropine, two of the six patients stopped urinating during the night. The frequency of nighttime urination decreased markedly (to 2-3 times per week) in three other patients. It was later discovered that the patient who did not respond had had a urethral dilation procedure to relieve strictures and had a history of repeated bladder infections.

We believe that our limited results are important, and if they are replicated in a larger sample, this treatment will contribute to the comfort of many long-term psychiatric patients. It must be emphasized that 4 mg of benztropine at 8:00 p.m. was required to control the bed-wetting, and there were no other changes in the patients' medications or treatment plans. All of these patients had been taking benztropine, 2 mg p.o. at 8:00 a.m. and 8:00 p.m., and the increase of the evening dose to 4 mg was necessary to achieve the desired effect. Since benztropine is a long-acting anticholinergic, we found that the morning dose could be eliminated for three of our patients. Large doses of benztropine can cause cognitive difficulties, particularly in elderly patients.

We are presently conducting a systematic evaluation of benztropine in a larger sample of nocturnal bed-wetters in order to evaluate more thoroughly both the therapeutic effect and the potential side effects of this new treatment.

### REFERENCES

1. Hu T-W, Igou JF, Kaltreider DL, et al: A clinical trial of a behavioral therapy to reduce incontinence in nursing homes. *JAMA* 1989; 261:2656-2662
2. Richelson E: Neuroleptic affinities for human brain receptors and their use in predicting adverse effects. *J Clin Psychiatry* 1984; 45:331-336

JEROME F. COSTA, M.D.  
JOHN SRAMEK, PHARM.D.  
RIMAL B. BERA, M.D.  
MARY BRENNEMAN, M.D.  
MARITA CRISTOBAL, M.D.  
*Norwalk, Calif.*

### Persistence of Psychiatric Symptoms in HIV Seropositive Persons

SIR: A number of neuropsychiatric and psychosocial complications, including suicide and suicide attempts, at all stages of HIV infection have been described (1, 2). Counseling is routinely provided to individuals when they are notified of their HIV seropositive status, but there are few data on the need for longer-term counseling or psychiatric follow-up.

The U.S. military services mandate periodic screening of active-duty individuals for the presence of antibodies to HIV. U.S. Air Force personnel who test positive receive annual medical and psychiatric examinations. We used standardized psychiatric rating scales and clinical examinations to compare rates of psychiatric illness and levels of psychological distress in 48 individuals who had just been notified that they were seropositive and in 41 individuals who had known for 1 year (mean=10.8 months, range=9-14 months). The examinations consisted of a psychiatric interview, a mental status examination, and administration of the Hamilton Rating Scale for Depression (3), the Hamilton Rating Scale for Anxiety (4), and the Michigan Alcoholism Screening Test (MAST) (5).

The 89 seropositive patients included 81 men and eight women. Their average age was about 30 years. Only four patients met the criteria of the Centers for Disease Control for AIDS. Significantly more ( $p=0.04$ ) of the initial evaluation patients ( $N=13$ , 27.1%, versus  $N=4$ , 9.8%) had abnormally high Hamilton depression scores (12 or higher). This finding suggests higher levels of dysphoria and psychological distress in the group that had just learned that they were seropositive.

However, an important number of psychiatric symptoms may also occur many months after a person has been notified of HIV seropositive status. Differences between the group just notified and the group that had known for a year failed to reach statistical significance on several variables: decreased libido (35.4% and 24.4%, respectively), suicidal ideation (25.0% and 17.1%), MAST score  $\geq 5$  (25.0% and 14.6%), and Hamilton anxiety score  $\geq 12$  (18.8% and 12.2%). No differences between the two groups in frequency of psychiatric diagnoses approached statistical significance. The most common diagnoses for both groups were personality disorder (29.2% for the just-notified group and 36.6% for the group that had known for a year), adjustment disorder (22.9% and 17.1%, respectively), simple phobia (20.8% and 17.1%), hypoactive sexual desire disorder (12.5% and 9.8%), major depression (8.3% and 2.4%), alcohol abuse (12.5% and 7.3%), and organic mental disorder (10.4% and 2.4%). However, the percentage of patients who expressed a

desire not to be returned to active duty was almost double in the group that had known their HIV status for a year (46.3% versus 25.0%;  $p=0.04$ ).

There are several ways in which the two groups could differ that might have affected the results: demographic composition, stage of physical illness, number of psychosocial stressors, perception of the quality of social support, psychiatric predisposition, and degree of CNS involvement. However, the results of this study suggest the need for follow-up counseling and availability of long-term psychiatric care. Clinicians who refer patients for HIV screening and those who administer HIV screening programs should consider approaches to address and prevent the long-term as well as the short-term emotional sequelae in patients who learn of their HIV seropositive status.

## REFERENCES

1. Faulstich ME: Psychiatric aspects of AIDS. *Am J Psychiatry* 1987; 144:551-556
2. Rundell JR, Paolucci SL, Beatty DC, et al: Psychiatric illness at all stages of human immunodeficiency virus infection (letter). *Am J Psychiatry* 1988; 145:652-653
3. Hamilton M: A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960; 23:56-62
4. Hamilton M: The assessment of anxiety states by rating. *Br J Med Psychol* 1959; 32:50-55
5. Selzer ML, Vinokur A, Von Rooijen L: A self-administered short Michigan Alcoholism Screening Test (MAST). *J Stud Alcohol* 1975; 36:117-124

JAMES R. RUNDELL, M.D.  
Bethesda, Md.  
GEORGE R. BROWN, M.D.  
San Antonio, Tex.

## Low Serum Albumin Levels and Risk of Delirium

SIR: We previously reported an association between an albumin level below 3.0 g/dl and delirium in patients with liver disease (1). In these patients, discriminant analysis revealed that albumin level, degree of EEG slowing, and Trail Making Test B scores were the three most important discriminators of delirious patients. Levkoff et al. (2) extended our findings by reporting a greater risk of delirium when serum albumin levels were below 3.5 g/dl in elderly patients hospitalized for a variety of medical and surgical conditions.

We feel that there are a number of reasons that a low serum albumin level contributes to the risk of delirium. A low albumin level occurs in many chronic conditions and reflects the severity of the underlying disease rather than simply malnutrition (3). Older patients with severe underlying illness and multiple medical conditions are at greater risk for delirium during hospitalization (4).

Delirium occurs more frequently among patients who are already demented. Studies of delirium have shown that the risk is three to four times greater among patients with prior cognitive impairment (4). Serum albumin levels are lower in demented patients than in age- and sex-matched control subjects (5), which may account for some of the association of a low serum albumin level with delirium.

Finally, albumin has an important role in binding and transporting many medications. Any reduced capability to bind such drugs, particularly those with CNS side effects, will result in higher free drug concentrations and, therefore, more potential for precipitating delirium.

We recommend routine screening of serum albumin levels in patients who are medically ill, especially the elderly, to help assess their risk of delirium. Patients at higher risk should be monitored carefully, e.g., by using cognitive screening tests. Prompt diagnosis and management of delirium may reduce the greater length of hospitalization and high mortality that have been associated with this condition.

## REFERENCES

1. Trzepacz PT, Brenner RP, Coffman G, et al: Delirium in liver transplantation candidates: discriminant analysis of multiple test variables. *Biol Psychiatry* 1988; 24:3-14
2. Levkoff SE, Safran C, Cleary PD, et al: Identification of factors associated with the diagnosis of delirium in elderly hospitalized patients. *J Am Geriatr Soc* 1988; 36:1099-1104
3. Friedman PJ, Campbell AJ, Caradoc-Davies TH: Hypoalbuminemia in the elderly is due to disease, not malnutrition. *J Clin Experimental Gerontology* 1985; 7:191-203
4. Francis J, Martin D, Kapoor W: Predictors of delirium in elderly medical patients. *Clin Res* 1989; 37(2):786A
5. Elcvaaara I, Maury CP, Palo J: Serum amyloid protein, albumin, and prealbumin in Alzheimer's disease and in demented patients with Down's syndrome. *Acta Neurol Scand* 1986; 74:245-250

PAULA T. TRZEPACZ, M.D.  
JOSEPH FRANCIS, M.D., M.P.H.  
Pittsburgh, Pa.

## Exposure to Ultraviolet B Radiation During Phototherapy

SIR: Phototherapy has increasingly become accepted as an effective treatment for seasonal affective disorder (1). Limited work, however, has been done on the spectral nature of phototherapy (2). Duro-Test "Vita-Lite" or General Electric "Cool White" fluorescent tubes, which produce ultraviolet and visible light, have been commonly used by researchers. Overexposure to ultraviolet A radiation may contribute to formation of nuclear cataracts, but a quantitative relationship between exposure and this risk has not been developed. Because overexposure to ultraviolet B radiation was recently quantified as a risk factor for cortical cataracts (3), we wished to calculate the potential risk for patients receiving phototherapy. We therefore analyzed manufacturer-supplied data on the ultraviolet B irradiance of the two commercially available bulbs we have mentioned.

For purposes of risk calculation, we postulated that in a worst-case scenario an overly enthusiastic patient would stare directly at a 2500-lux light source for 2 hours daily, although in one paradigm investigators have asked patients to glance at such a light source only once or twice a minute for at least 2 hours per day (4). (Exposure to 10,000 lux of light allows similar amounts of radiation in one-half hour a day.) In the region of 285-325 nm, the Vita-Lite produces an irradiance of 5.5  $\mu\text{W}/\text{cm}^2$ , and the Cool White, 5.8  $\mu\text{W}/\text{cm}^2$ . Assuming that biological effectiveness depends on a wavelength similar to that for skin erythema (5), the effective irradiances for these bulbs in this region are 2.2  $\mu\text{W}/\text{cm}^2$  for the Vita-Lite and 2.6  $\mu\text{W}/\text{cm}^2$  for the Cool White. Staring directly at the lamps for 2 hours daily, 90 days a year, the patient would therefore receive 1.4  $\text{J}/\text{cm}^2$  per year of ultraviolet B radiation from the Vita-Lite or 1.7  $\text{J}/\text{cm}^2$  per year from the Cool White. A recent study of Maryland watermen (whose occupation exposes them to high levels of ultraviolet light) has documented that exposure to lesser amounts of ultraviolet B (1.3  $\text{J}/\text{cm}^2$  per year) over many years can in-

crease the risk of developing cortical cataracts (of at least grade 2 opacity) from approximately 5% to over 10% (3).

Several conclusions are suggested by these data. First, in the ultraviolet B region of the spectrum, Cool White and Vita-Lite tubes deliver similar amounts of radiation. Second, clinicians may now wish to inform patients of the potential for development of cortical cataracts after many years of excessive exposure to ultraviolet light from fluorescent bulbs (as well as the sun). Actual exposure to ultraviolet B radiation through phototherapy is likely to be considerably less than our calculated values, given that patients spend the majority of their phototherapeutic sessions receiving the light at an indirect angle and given that emissions fall off as bulbs age. Nevertheless, patients should be instructed not to stare directly at the lights for long periods of time. With an adverse effect from ultraviolet radiation unlikely but possible, researchers in the field of phototherapy would do well to study the effects of phototherapy delivered through ultraviolet-absorbing filters.

## REFERENCES

1. Rosenthal NE, Sack DA, Gillin JC, et al: Seasonal affective disorder: a description of the syndrome and preliminary findings with light therapy. *Arch Gen Psychiatry* 1984; 41:72-80
2. Rosenthal NE, Sack DA, Skwerer RG, et al: Phototherapy for seasonal affective disorder. *J Biological Rhythms* 1988; 3:101-120
3. Taylor HR, West SK, Rosenthal FS, et al: Effect of ultraviolet radiation on cataract formation. *N Engl J Med* 1988; 319:1429-1433
4. Jacobsen FM, Rosenthal NE: Seasonal affective disorder, in *Depression and Mania: A Comprehensive Textbook*. Edited by Georgotas A, Cancro R. New York, Elsevier Science, 1988
5. Berger DS: The sunburning ultraviolet meter: design and performance. *Photochem Photobiol* 1976; 24:587-593

DAN A. OREN, M.D.  
FRANK S. ROSENTHAL, PH.D.  
NORMAN E. ROSENTHAL, M.D.  
MORRIS WAXLER, PH.D.  
THOMAS A. WEHR, M.D.  
*Bethesda, Md.*

## Diagnostic Criteria for Epilepsy-Related Mental Changes

SIR: Epilepsy may be associated with a complex mixture of psychiatric disorders. Most prominent are rapid shifts in mood, with predominant depression and episodic irritability that occasionally becomes explosive (1, 2). Schizophrenia-like episodes with paranoia, hallucinations, and/or delusions are occasionally associated with epilepsy (3, 4). Recurrent attacks of anxiety, symptoms of somatization disorder, and episodes of amnesia and/or confusion are experienced; in fact, many of the phenomena described as characterizing psychiatric disorders can be present in the epileptic patient. It is standard practice to separate the recognized neurologic seizure manifestations from the psychiatric symptoms; the latter are catalogued as the psychiatric disorders of nonepileptic patients. Closer scrutiny, however, suggests important differences between the mental abnormalities of epileptic patients and those present in nonepileptic psychiatric patients.

Thus, the mood changes associated with epilepsy differ from those of manic-depressive illness because of their rapid shifts (rapid cycling). Schizophrenia-like symptoms occur in patients with epilepsy who tend to be very emotional but are

not schizoid and relate well to others. Overall, the mental changes in epilepsy tend to be atypical for the psychiatric disorders they resemble, they tend to occur in highly episodic form (often with sudden onset and termination), and they tend to be pleomorphic in a given patient, presenting in clusters or in succession. A precise, traditional diagnostic classification is usually not possible. In addition, patients with epilepsy—particularly those with long-standing illness—may manifest a range of more subtle yet relatively stable personality and behavioral changes (hyperemotionality, viscosity, hyposexuality) that have been called interictal personality traits (1).

*DSM-III-R* presents a number of descriptions of organic mental disorders (organic mood disorder, organic delusional disorder, organic hallucinosis, organic anxiety disorder, amnesic disorder, organic personality disorder) that can be used to approximate the syndromes noted in patients with seizure disorders. Such a categorization lacks specificity and is only tangentially descriptive. We would like to suggest a separate classification for the psychiatric complications of chronic seizure disorders and present the following as a working model.

*Neurobehavioral Disorders of Epilepsy*

1. Mood disorder (dysphoric, euphoric, rapid cycling, mixed)
2. Irritable-impulsive disorder
3. Schizophreniform disorder (paranoid, delusional, hallucinatory)
4. Anxiety disorder (panic, phobic, generalized)
5. Amnesic-confusional disorder
6. Somatoform disorder (pseudoseizures, pain)
7. Personality disorder (viscous, hyperemotional, hypersexual)
8. Compound (more than two of the preceding categories)
9. Not otherwise specified

In this classification the term "neurobehavioral" refers to the underlying organic substrate but does not claim a specific anatomic/functional basis as is implied by currently used terms such as "temporal lobe syndrome" or "limbic mental syndrome."

Some of the symptoms characteristic of the neurobehavioral syndrome of epilepsy may be present in patients who do not have overt clinical seizures (and therefore do not rate classification as epileptic) but do have evidence of organic brain disease (e.g., head injury, encephalitis, cerebrovascular accident). Until the phenomena of these disorders are better defined, it would be best to continue listing the organic factors on axis III, with the anticipation that future investigation will demonstrate a similar hierarchy of mental changes based on organic factors which may give rise to subclinical seizure disturbances.

## REFERENCES

1. Blumer D: Epilepsy and disorders of mood, in *Neurobehavioral Problems in Epilepsy*, Advances in Neurology. Edited by Smith DB, Treiman DM, Trimble MR. New York, Raven Press (in press)
2. Mendez MF, Cummings JL, Benson DF: Depression in epilepsy: significance and phenomenology. *Arch Neurol* 1986; 43:766-770
3. Perez MM, Trimble MR: Epileptic psychosis—diagnostic com-

parison with process schizophrenia. *Br J Psychiatry* 1980; 137: 245-249

4. Slater E, Beard AW: The schizophrenia-like psychoses of epilepsy. *Br J Psychiatry* 1963; 109:95-150

DIETRICH BLUMER, M.D.  
VERNON NEPPE, M.D., PH.D.  
D. FRANK BENSON, M.D.  
*Memphis, Tenn.*

### Psychiatric Reaction to Ketoconazole

SIR: We would like to comment on the letter to the Editor "Adverse Psychiatric Reaction to Ketoconazole" by R.Z. Fisch, M.D., and A. Lahad, M.D. (1). They interpreted the hallucinations reported by a patient 1-2 hours after ingesting ketoconazole as "a genuine, if idiosyncratic, reaction" to the drug, apparently due to CNS involvement. However, ketoconazole does not cross the intact blood-brain barrier, and it crosses to only a limited extent in fungal meningitis (2).

An alternative explanation for the onset of psychiatric symptoms could be the action of ketoconazole as a steroid inhibitor (3); that is, a 400-mg oral dose causes a transient decrease in plasma cortisol levels. On the other hand, the drug is used as a palliative treatment of Cushing's syndrome with impressive clinical results, including regression of psychiatric symptoms (3). Chronic states of hypocortisolism, such as Addison's disease, may be associated with psychotic symptoms, including hallucinations (4, 5), even though depression is the most common symptom (6). Perturbation of the hypothalamic-pituitary-adrenal axis due to adrenal enzymatic inhibition by ketoconazole may, therefore, play a role in the precipitation of psychiatric symptoms in predisposed individuals.

It should be pointed out that according to the authors' description in their case report, the patient was not free of psychopathology (hypomanic temperament, personality problems) as was claimed in the conclusion of their letter. In large samples of patients treated with high doses of ketoconazole (800-2000 mg/day) for systemic mycoses, endocrine conditions, or hormone-producing tumors, psychiatric reactions have never been reported. We agree with the authors about the very "idiosyncratic" nature of the drug reaction they reported.

### REFERENCES

1. Fisch RZ, Lahad A: Adverse psychiatric reaction to ketoconazole (letter). *Am J Psychiatry* 1989; 146:939-940
2. Daneshmend TK, Warnock DW: Clinical pharmacokinetics of ketoconazole. *Clin Pharmacokinet* 1988; 14:13-44
3. Sonino N: The use of ketoconazole as an inhibitor of steroid production. *N Engl J Med* 1987; 317:812-818
4. Engel GL, Margolin SG: Neuropsychiatric disturbances in internal disease. *Arch Intern Med* 1942; 70:236-259
5. McFarland HR: Addison's disease and related psychoses. *Compr Psychiatry* 1963; 4:90-95
6. Fava GA, Sonino N, Morphy MA: Major depression associated with endocrine disease. *Psychiatr Dev* 1987; 4:321-348

NICOLETTA SONINO, M.D.  
*Padova, Italy*  
GIOVANNI A. FAVA, M.D.  
*Bologna, Italy*

### Dr. Fisch and Dr. Lahad Reply

SIR: Dr. Sonino and Dr. Fava call attention to the point that ketoconazole does not cross the intact blood-brain barrier and that our patient's symptoms may be explained as other than a direct drug reaction. We agree that ketoconazole's action as a steroid inhibitor may play a role in the precipitation of psychiatric symptoms in predisposed individuals. On the other hand, we cannot dismiss the possibility that small amounts of the drug or its metabolites do enter the CNS and produce typical CNS side effects (headaches, dizziness, somnolence, photophobia).

The possibility that our patient was not free of psychopathology before the ingestion of the drug does not exclude a genuine adverse reaction. The symptoms of his drug reaction were clearly different from his usual experience and appeared only in connection with that drug. The fact that psychiatric reactions to ketoconazole have not been reported before and that the manifestation of this drug reaction is very unusual is what makes this case interesting.

R.Z. FISCH, M.D.  
A. LAHAD, M.D.  
*Jerusalem, Israel*

### Acetazolamide as a Control for CO<sub>2</sub>-Induced Panic

SIR: A recent article by Roy J. Mathew, M.D., and associates (1) explored the possibility that an increased CO<sub>2</sub> level in the CNS can trigger panic attacks in patients with panic disorder. Thirteen panic disorder patients were given intravenous acetazolamide, a carbonic anhydrase inhibitor, and 10 panic disorder patients received normal saline infusion in a double-blind, random design. The authors claimed that acetazolamide caused brain hypercarbia, because they found an increase in cerebral blood flow. Since none of the subjects who were given acetazolamide panicked, the authors felt justified in disputing the CO<sub>2</sub> hypersensitivity theory of panic.

We believe that this study cannot address this theory, let alone refute it. The authors insisted, in spite of their own extensive references to the contrary, that "there is little doubt about the hypercarbia and acidosis induced by acetazolamide." In fact, the only evidence supporting this assumption was increased cerebral blood flow. However, one of the articles in the authors' own reference list states, "AZ caused a rapid vasodilation in the brain and over a wide range of pCO<sub>2</sub>'s . . . this agent has a local vasodilator effect on the cerebral arterioles, unrelated to its specific effects as a carbonic anhydrase inhibitor" (2). Therefore, why assume that the changes in cerebral blood flow were caused by hypercarbia?

Acetazolamide penetrates the blood-brain barrier very slowly, so much of the effect that Dr. Mathew and associates noted during their approximately 10 minutes of cerebral blood flow measurements may not even have been due to acetazolamide. They failed to note that carbonic anhydrase catalyzes a reversible reaction between bicarbonate and CO<sub>2</sub>; the direction of the reaction depends on the law of mass action. Inhibiting the enzyme will not affect the direction of the reaction. Hypocarbia or hypercarbia will result depending on the physiological state of the subject.

The authors' own data do not support the inference of brain hypercarbia, since none of the subjects who received acetazolamide experienced the slightest respiratory change (the dizziness can easily be explained by vasodilation). Had brain hypercarbia indeed developed, there should have been



the usual increase in tidal volume and respiratory rate. Since there is no evidence that hypercarbia developed, the experiment did not address CO<sub>2</sub> anxiogenesis.

Acetazolamide is not an ideal choice for this kind of experiment because it causes multiple physiological changes, whereas its CNS action is mostly unknown. This study leaves open the possibility that panic disorder patients are hypersensitive to CO<sub>2</sub> (3).

## REFERENCES

1. Mathew RJ, Wilson WH, Tant S: Responses to hypercarbia induced by acetazolamide in panic disorder patients. *Am J Psychiatry* 1989; 146:996-1000
2. Hauge A, Nicolaysen G, Thoresen M: Acute effects of acetazolamide on cerebral blood flow in man. *Acta Physiol Scand* 1983; 117:233-239
3. Papp LA, Goetz R, Cole R, et al: Hypersensitivity to carbon dioxide in panic disorder. *Am J Psychiatry* 1989; 146:779-781

DONALD F. KLEIN, M.D.  
LASZLO A. PAPP, M.D.  
JACK M. GORMAN, M.D.  
New York, N.Y.

## Dr. Mathew Replies

SIR: Dr. Klein and associates argue that acetazolamide does not induce hypercarbia in the brain, and therefore it cannot be used to test increased brain sensitivity to CO<sub>2</sub> in panic disorder patients. I am grateful to them for giving me the opportunity to express my views on the subject in some detail.

An extensive volume of literature is available on carbonic anhydrase and its inhibition (1). The vast majority of research reports indicate that inhibition of carbonic anhydrase by acetazolamide results in metabolic acidosis and CO<sub>2</sub> retention all over the body, including the brain. The view that slow penetration of the blood-brain barrier by acetazolamide argues against drug-induced CO<sub>2</sub> retention in the brain reflects unfamiliarity with the physiology of CO<sub>2</sub> removal by neural tissues. Neurons do not contain carbonic anhydrase, unlike the glia and choroid plexus. CO<sub>2</sub> removal from the neurons is facilitated by the carbonic anhydrase contained in RBCs, the inhibition of which will result in CO<sub>2</sub> retention in neurons. Acetazolamide inhibits RBC carbonic anhydrase within moments; the drug does not need to penetrate the blood-brain barrier to accomplish this (1).

Several indirect sources of evidence suggest hypercarbia after administration of acetazolamide. Acetazolamide has been reported to lessen symptoms that occur when arterial CO<sub>2</sub> levels are rapidly reduced by the use of mechanical ventilators in patients with chronic respiratory failure. Acetazolamide (and other carbonic anhydrase inhibitors, such as methazolamide) and CO<sub>2</sub> have similar CNS effects (depression of spinal monosynaptic reflexes in the cat, decreased EEG spikes in the cat and the monkey, and an anticonvulsant effect) (1).

Once lung carbonic anhydrase is inhibited, end tidal CO<sub>2</sub> ceases to be a reliable index of arterial levels. Krintel et al. (2) demonstrated significant hypercarbia in peripheral tissues, central venous blood, and arterial blood after the administration of 15 mg/kg of acetazolamide to 10 patients with chronic obstructive pulmonary disease. Mithoefer and Davis (3) detected an increase in CO<sub>2</sub> tension in arterial blood and

subcutaneous gas pockets (created by injecting air into subcutaneous tissue) in rats after carbonic anhydrase inhibition. Meyer and Gotoh (4) observed marked increases (often exceeding 20 mm Hg) in cerebral cortical PCO<sub>2</sub> measured with CO<sub>2</sub> electrodes after acetazolamide was given to monkeys and cats. Brzezinski et al. (5) noted significant increases in CSF CO<sub>2</sub> after acetazolamide was administered to cats and rats. Kennealy et al. (6) found significant increases in brain CO<sub>2</sub> (measured with an intracerebral Teflon-coated steel catheter and mass spectrometer) after administration of acetazolamide in every dog they studied. I do not know of a single study that has failed to find tissue hypercarbia immediately after administration of acetazolamide.

Subjects who received acetazolamide in our study were asked to breathe regularly, since this is of fundamental importance to cerebral blood flow measurement with the xenon-133 inhalation technique. This may explain the absence of drug-induced changes in respiratory rate.

While there is some uncertainty about factors other than hypercarbia that are responsible for postacetazolamide cerebral vasodilation (reference 38 in our article), there is little doubt concerning the hypercarbia and metabolic acidosis. Absence of acetazolamide-induced hypercarbia is therefore unlikely to be the explanation for the drug's failure to precipitate attacks.

## REFERENCES

1. Maren TH: Carbonic anhydrase: chemistry, physiology and inhibition. *Physiol Rev* 1967; 47:595-781
2. Krintel JJ, Haxholdt OS, Berthelsen P, et al: Carbon dioxide elimination after acetazolamide in patients with chronic obstructive pulmonary disease and metabolic alkalosis. *Acta Anaesthesiol Scand* 1983; 27:252-254
3. Mithoefer JC, Davis JS: Inhibition of carbonic anhydrase: effect on tissue gas tensions in the rat. *Proc Soc Exp Biol Med* 1958; 98:797-801
4. Meyer JS, Gotoh F: Interaction of cerebral hemodynamics and metabolism. *Neurology* 1961; 11(2):46-65
5. Brzezinski J, Kjallquist A, Siesjo BK: Mean carbon dioxide tension in the brain after carbonic anhydrase inhibition. *J Physiol (Lond)* 1967; 188:13-23
6. Kennealy JA, McLennan JE, Fields C, et al: Acetazolamide and cerebral oxygenation in dogs. *Clin Invest Med* 1984; 7:103-108

ROY J. MATHEW, M.D.  
Durham, N.C.

## Use of Animals in Research on Panic Disorder

SIR: The experiments of Gayle Sunderland, Ph.D., and associates (1) represent a troubling example of the readiness of researchers to use animals with no clear goal in sight. These authors treated monkeys with imipramine, alprazolam, or placebo, then infused sodium lactate, and observed that the distress they had been able to cause the monkeys was reduced by the two drugs. All of this, of course, can be done with human subjects.

It appears that this research was intended to be part of an effort to model panic disorder in animals. Modeling should be predicated on clear-cut need, which was not indicated in the research report. The time is long past when such experiments, which cause considerable distress in animals, are tolerable. The 1985 amendment to the Animal Welfare Act requires attention to the psychological needs of primates.

While the scientific community has managed to stall the implementation of the regulations pursuant to that amendment, it should have shared its goals. These vaguely rationalized and obviously distressing experiments should not have been done.

## REFERENCE

1. Sunderland G, Friedman S, Rosenblum LA: Imipramine and alprazolam treatment of lactate-induced acute endogenous distress in nonhuman primates. *Am J Psychiatry* 1989; 146:1044-1047

NEAL D. BARNARD, M.D.  
Washington, D.C.

## Dr. Rosenblum and Dr. Friedman Reply

SIR: The history of medicine is replete with well-recognized examples of the significant role of animal research in providing us with a fundamental understanding of various disease states and with the capacity to develop the breadth of therapeutic techniques central to the level of medical care we enjoy today. We recognize that there have always been those who feel, as Dr. Barnard does, that if relevant research can be done with human subjects, animals should be spared participation in those types of investigation. But notwithstanding the importance of human research subjects, as we indicated in the introduction to our article, for most of us, there is a range of investigations relating to "etiology, mechanisms, and treatment" of various disorders for which the use of human subjects is neither feasible nor ethically possible. Given current estimates that panic disorder has a lifetime prevalence rate of 1.4%, that several times this number of people have less severe forms of the disease, and that suicide is not an uncommon sequela of the problem (1, 2), there is a clear need to pursue a variety of approaches to this disorder.

Development of an appropriate animal model will considerably facilitate systematic examination of such issues as the possible roles of altered neurotransmitter levels and particular developmental experiences in the etiology of the disease, as well as the potential efficacy of a variety of treatment modalities, including new pharmacological agents. Contrary to Dr. Barnard's statements, these perspectives were detailed in the Discussion section of our article. This certainly is not meant to imply that all proposed forms of research on animals will be able to meet society's ethical and legal standards for humane treatment of animal subjects. However, the procedures used in our study were in keeping with the Animal Welfare Act of 1985 and were reviewed and found appropriate by our Institutional Animal Care and Use Committee as well as by the *Journal* reviewers before publication of the article. As responsible animal investigators, we actively support efforts to maintain the highest standards of humane treatment of our subjects, but we are unwilling to callously defer humanely structured research that holds the promise of alleviating the suffering of large numbers of our fellow citizens.

## REFERENCES

1. Weissman MM, Klerman GL, Markowitz JS, et al: Suicidal ideation and suicide attempts in panic disorder and attacks. *N Engl J Med* 1989; 321:1209-1214
2. Robbins LN, Helzer JE, Weissman MM, et al: Prevalence of

specific psychiatric disorders in three sites. *Arch Gen Psychiatry* 1984; 41:949-953

LEONARD A. ROSENBLUM, PH.D.  
STEVEN FRIEDMAN, PH.D.  
Brooklyn, N.Y.

## Left-Handedness and Ventricle Size in Schizophrenic Patients

SIR: We were intrigued by the recent report "Association of Left-Handedness With Ventricle Size and Neuropsychological Performance in Schizophrenia" (1). In an attempt to replicate the findings of this study, we reviewed the records of patients admitted to the Neuropsychiatric Research Hospital of the National Institute of Mental Health. One hundred fifty-nine patients met the *DSM-III* or *DSM-III-R* criteria for undifferentiated or paranoid schizophrenia; their files contained extensive neuropsychological data as well as ventricle-brain ratio (VBR) measurements made on CT scans.

Of the 159 patients, 14 (9%) wrote with their left hands. This is a proportion that approximates the rate of left-handedness in the normal population (2). There was no significant difference between the groups on VBR measurements ( $t=0.35$ ,  $p>0.70$ ). We also ran univariate tests on 20 neuropsychological variables, including all subtest and IQ measures from the WAIS-R; scores on the Category, Trail Making, and Tactual Performance tests and the Average Impairment Rating from the Halstead-Reitan Battery; results of a continuous performance test of vigilance and distractibility; and results of the Stroop Test. We were unable to identify a significant difference between right-handers and left-handers on any of the measurements.

Although some studies have identified greater rates of left-handedness in schizophrenia, Ms. Katsanis and Dr. Iacono did not note that others have failed to do so (3, 4). It is possible that a sample of schizophrenic patients in which left-handedness is markedly large may include a number of patients in which early cerebral impairment has led to "pathological" left-handedness. There is insufficient reason to presume, however, that the relationship between this type of cerebral impairment and the dysfunction associated with schizophrenia is anything more than epiphenomenal.

## REFERENCES

1. Katsanis J, Iacono WG: Association of left-handedness with ventricle size and neuropsychological performance in schizophrenia. *Am J Psychiatry* 1989; 146:1056-1058
2. Annett M: A classification of hand preference by association analysis. *Br J Psychol* 1970; 61:303-321
3. Taylor PJ, Dalton R, Fleming JJ: Handedness in schizophrenia. *Br J Psychiatry* 1980; 136:375-383
4. Taylor PJ, Dalton R, Fleming JJ, et al: Differences between two studies of hand preference in psychiatric patients. *Br J Psychiatry* 1982; 140:166-173

CHRISTOPHER RANDOLPH, PH.D.  
TERRY E. GOLDBERG, PH.D.  
JAMES GOLD, PH.D.  
DAVID G. DANIEL, M.D.  
DANIEL R. WEINBERGER, M.D.  
Washington, D.C.

## Ms. Katsanis and Dr. Iacono Reply

SIR: While the results presented by Dr. Randolph and associates are interesting, their data do not clearly contradict our finding that left-handed patients with schizophrenia have more cerebral dysfunction than right-handed patients. Our study and theirs differ in several important aspects that may account for the diverse findings.

Dr. Randolph and colleagues do not describe their schizophrenic sample beyond giving the subtype diagnoses and noting that the subjects were drawn from a special ward established for neuropsychiatric research. Our patients, all of whom met the *DSM-III* criteria for chronic schizophrenia, were carefully selected to eliminate elderly patients and patients with histories of substance dependence, tardive dyskinesia, and head trauma—all factors that could affect ventricular size and neuropsychological performance. Within the constraints imposed by our exclusionary criteria and the requirements for obtaining informed consent, our subjects either 1) were consecutive admissions from the sole extended-care psychiatric hospital serving a Canadian province or 2) represented the entire population of patients resident in boarding homes affiliated with our hospital. In addition, other factors that could affect test scores, such as educational level and medication status, did not differentiate the left- and right-handed groups. The special features of our sample may have been crucial to our obtaining differences between left- and right-handed patients, and our study participants were probably more representative of the population of young, chronic schizophrenic patients than those examined by Dr. Randolph and associates.

In order to examine differences between right-handed and left-handed groups, Dr. Randolph and colleagues performed univariate analyses. Our univariate tests also yielded nonsignificant differences between groups for the majority of the neuropsychological tests. However, examination of the data with multivariate analysis allows for the detection of significant trends in the data. Our multivariate analysis reached significance, and inspection of the group means revealed that for most of the neuropsychological tests, left-handers tended to perform more poorly than right-handers.

Besides the WAIS-R and the Trail Making Test (which neither we nor Dr. Randolph and associates found to differentiate groups), there was no overlap between the tests we used and those chosen by Dr. Randolph's group. The use of different types of tests, each of which taps different areas of functioning with varying sensitivity, could have contributed to our divergent findings.

Dr. Randolph and colleagues conclude their letter by arguing that we failed to report that certain investigators have not found greater rates of left-handedness in schizophrenia. However, our report was not meant to be a comprehensive examination of the relationship between left-handedness and schizophrenia. Rather, we wanted to examine the association of left-handedness and cerebral dysfunction in schizophrenia. According to our findings and those of others (1, 2), it appears that left-handed schizophrenic patients tend to have ventricular dilation and are neuropsychologically different from right-handed patients. Finally, if Dr. Randolph and associates have used the word "epiphenomenal" to mean "coincidental," we agree with them that further research is needed before any definite conclusions can be drawn regarding the association between "pathological" left-handedness and schizophrenia.

## REFERENCES

1. Andreasen NC, Dennert JW, Olsen SA, et al: Hemispheric asymmetries and schizophrenia. *Am J Psychiatry* 1982; 139: 427-430
2. Pearlson GD, Kim WS, Kubos KL, et al: Ventricle-brain ratio, computed tomographic density, and brain area in 50 schizophrenics. *Arch Gen Psychiatry* 1989; 46:690-697

JOANNA KATSANIS, M.A.  
WILLIAM G. IACONO, PH.D.  
Minneapolis, Minn.

## Legitimacy of Factitious Disorder Diagnoses

SIR: The article by Richard Rogers, Ph.D., and associates (1) questioning the legitimacy of the *DSM-III-R* diagnosis of factitious disorder with psychological symptoms is very interesting. Nevertheless, their perception of factitious disorders may stem from the forensic setting in which they work. The motivations of forensic patients are unusually complex and contaminated by attempts to avoid responsibility for behaviors which have led to legal charges. Because of these difficulties, *DSM-III-R* diagnoses must be used cautiously in forensic settings, and the diagnosis of factitious disorders may not be useful in these assessments.

I have noticed that I have seen more examples of factitious disorder with psychological symptoms over the past 3 years in a downtown general hospital than I had seen in 12 years in a psychiatric hospital and research institute. It may be that patients with factitious disorders, with either psychological or physical symptoms, selectively seek out general hospital settings so as to assume a patient role and not be perceived as "crazy."

In a typical case example, a 32-year-old woman was brought by the police to the emergency room; she appeared confused and lost. She said that she could not remember her name or address and appeared very sad. The next morning she still appeared depressed and almost mute. She nodded that she was married but could not remember her husband's name. When pressed for the truth, she responded, "I guess you know that I have a factitious disorder. I've been to 20 hospitals in the past 3 years. I don't know why I do it. If I don't stop I will lose my job and my marriage" (she had a husband and two children). Contact with the husband confirmed the patient's story and the absence of precipitating events or identifiable secondary gains.

In my experience, these patients come to general hospital emergency departments in the evening or on weekends with depression or other psychiatric symptoms and are admitted by a resident. On the ward such a patient may interact with the staff and other patients until the attending psychiatrist makes rounds and finds the patient depressed or confused and uncommunicative. Sometimes the charade ends when the physician confronts the patient with this observed discrepancy or a staff member recognizes the patient from having seen him or her at another hospital. The diagnosis is confirmed when the patient admits to pretending to be mentally ill but can give no explanation for doing this. The secondary gains of malingering are absent.

It is my impression that many patients with factitious disorders go to emergency rooms in teaching general hospitals where anonymity is almost assured. These are people who have a need to be patients. Thus, in a general psychiatric setting, factitious disorder is a useful diagnostic label and an accurate description of a common syndrome that does not

meet the criteria for a disease. It appears to have both conscious and unconscious determinants. In forensic settings and in civil litigation assessments, the secondary gains are such obvious and important motivating factors that malingerers should be the preferred diagnosis.

## REFERENCE

1. Rogers R, Bagby RM, Rector N: Diagnostic legitimacy of factitious disorder with psychological symptoms. *Am J Psychiatry* 1989; 146:1312-1314

BRIAN F. HOFFMAN, M.D., F.R.C.P.(C)  
Toronto, Ont., Canada

## Dr. Rogers and Dr. Bagby Reply

SIR: Dr. Hoffman's suggestion—based entirely on his impressions and experiences—that factitious disorder patients selectively seek out general hospitals (in particular, emergency rooms of teaching hospitals) in the evening or on weekends is an interesting and empirically testable hypothesis. During our literature search, however, we were unable to locate any studies to support or negate this hypothesis. Nevertheless, we would certainly encourage Dr. Hoffman and other researchers to pursue the issue.

Of course, the methodological problems that investigators will encounter in conducting such a study are very difficult, if not insurmountable, at least on the basis of the current diagnostic criteria for factitious disorder. Presumably, such a study would require that a group of clinical raters reach a consensus regarding the diagnosis of factitious disorder, an unenviable task given the low kappa coefficients for interrater agreement that have been reported in the *DSM-III* field studies. Part of the reason for the low kappa coefficients may be located in the difficulty of ruling out "intrapsychic needs" in the absence of external incentives. Merely contacting a spouse to corroborate a story or cursorily examining possible external incentives is insufficient in assigning a diagnosis for research purposes. Extensive interviewing of the client, the client's family, and significant others in both the workplace and the social environs is absolutely essential for establishing a reliable diagnosis of this disorder.

Given the difficulties in conducting such a study, it should be clear that Dr. Hoffman's implicit contention that our perception of factitious disorders may be clouded by our work with forensic patients dodges the unresolved issues concerning the diagnostic legitimacy of factitious disorders. While we agree that it is most difficult to disentangle the complex web of motivations that typify forensic patients, basic principles of diagnosis are not invariable across different patient samples. In the two cases that we provided, both patients had presented a similar clinical picture in a variety of settings. We doubt that factitious disorders are context-specific.

Our essential argument, then, is that the rationale that underlies and informs the diagnostic criteria for factitious disorder is, at present, logically indefensible and empirically unfounded. Deferring to sample characteristics does not address the fundamental diagnostic conundrums of factitious disorder.

RICHARD ROGERS, PH.D.  
R. MICHAEL BAGBY, PH.D.  
Toronto, Ont., Canada

## Comorbidity of Psychiatric Disorders in Adolescents

SIR: Oscar G. Bukstein, M.D., M.P.H., and associates (1) did an excellent job of reviewing the problems of dual diagnosis in adolescents. There are, however, two further points I wish to make. First, in discussing the methodological problems of research into the comorbidity of substance abuse and other psychiatric disorders, the authors failed to mention the age of the adolescent as a critical factor in determining what is use or abuse of a substance. A 14-year-old high school freshman who drinks alcohol on weekends is very different from an 18-year-old college freshman who drinks alcohol on weekends. Research needs to account for the rapidly changing developmental norms during adolescence. Second, in reviewing 5 months of consecutive discharges from our hospital-based chemical dependency treatment program, I found that 90% (89 of 99) adolescents discharged with dual diagnoses also had second and third substances of abuse or dependence. Thus, in our population of dual-diagnosis adolescents, we have the added complication of symptoms caused by more than one substance of abuse and the interactions of these substances with each other. As more research on dual diagnosis in adolescence is done, abuse of multiple drugs needs to be carefully studied.

I am pleased that the complex problems of adolescent substance abuse and psychiatric disorders is starting to be seriously studied.

## REFERENCE

1. Bukstein OG, Brent DA, Kaminer Y: Comorbidity of substance abuse and other psychiatric disorders in adolescents. *Am J Psychiatry* 1989; 146:1131-1141

THOMAS P. CORNWALL, M.D.  
Raleigh, N.C.

SIR: The article "Comorbidity of Substance Abuse and Other Psychiatric Disorders in Adolescents" by Oscar G. Bukstein, M.D., and colleagues is an excellent review of the clinical and theoretical aspects of dual diagnosis in adolescents. The authors discussed the methodological difficulties encountered in research into comorbidity and proposed several research directions. I would like to comment on a few additional methodological difficulties and to make further recommendations for research.

The Research Diagnostic Criteria (RDC) for substance use disorder need to be validated for use with adolescents. Dr. Bukstein and associates reported that there is a lack of studies confirming the validity and reliability of the *DSM-III-R* criteria for substance use disorder in adolescents and recommended the establishment of reliable diagnostic criteria for use with these patients. These recommendations need also to be applied to the RDC for substance abuse. On the other hand, many of the questionnaires used in structured interviews—e.g., the Schedule for Affective Disorders and Schizophrenia for School-Age Children (1)—have questions designed to accommodate diagnoses made with the *DSM-III-R* criteria and the RDC. These questions designed to evaluate substance use disorders also need to be validated for use in the adolescent population.

Adolescents with dual diagnoses need to be compared with adolescents who have only one of the comorbid diagnoses. This may help in understanding the relationship between the coexistent illnesses. The presence of a secondary disorder (e.g., substance use disorder) can often complicate the clinical



cal picture of a primary disorder (e.g., depression). The clinical symptoms, biological correlates, course, response to treatment, and prognosis can be altered by the secondary disorder (2). Patients with primary disorders who develop comorbid disorders may, in fact, represent a subgroup of patients who are different from those who do not develop a secondary illness. The authors mentioned that certain patterns of comorbidity are intrinsic to an illness and that a valid nosology needs to consider comorbidity as a possible basis for subtypes. These are sufficient reasons for including comparative studies in future research. Such studies may help us understand the effect of secondary disorders on primary illnesses. These comparisons may also provide information about intrinsically different subgroups of patients.

The use of longitudinal studies should provide important information regarding the frequency and nature of comorbidity in specific clinical subgroups of patients. The authors suggested the continuous examination of high-risk children (e.g., children of alcoholics). Longitudinal studies should also be applied to patients who have primary disorders without comorbidity. Individuals with different psychiatric illnesses have different risks of developing substance abuse. Also, substance abusers are at high risk for developing specific psychopathologies (3). Moreover, individuals with the same clinical syndrome (e.g., depression) may have different risks of developing comorbidity. Cross-sectional observation studies of a group of patients may not detect the subgroup that will later develop a comorbid illness. However, longitudinal studies could, retrospectively, provide information about the risk factors associated with the development of a secondary illness. Such information may help in the early detection of high-risk subgroups of patients and the proper application of preventive measures.

## REFERENCES

1. Orvaschel H, Puig-Antich J: Schedule for Affective Disorders and Schizophrenia for School-Age Children, Epidemiologic Version (Kiddie-SADS-E). Pittsburgh, Western Psychiatric Institute and Clinic, 1987
2. Rounsaville BJ, Dolinsky ZS, Babor TF, et al: Psychopathology as a predictor of treatment outcome in alcoholics. *Arch Gen Psychiatry* 1987; 44:505-513
3. McLellan AT, Childress AR, Woody GE: Drug abuse and psychiatric disorders: role of drug choice, in *Substance Abuse and Psychopathology*. Edited by Alterman AI. New York, Plenum, 1985

MICHEL J. CALACHE, M.D.  
*Springfield, Ill.*

## Dr. Bukstein and Associates Reply

SIR: Dr. Cornwall raises two salient points about research into comorbid disorders in adolescents. The first comment deals with the lack of a valid nosology for adolescent substance abuse and dependence vis-à-vis adult criteria for these disorders. One must wonder how we can truly study comorbidity—or any aspect of adolescent substance use and abuse—before determining what constitutes pathological use. The second comment deals with the use or abuse of multiple substances. The use of multiple substances by many adolescents demands careful research into the chronology of comorbid behaviors and symptoms.

Dr. Calache's comments reinforce the importance of care-

ful methodology in future studies of adolescent substance abuse and comorbidity. Again, the lack of a valid nosology and instruments to measure substance use pathology are evident. The possibility that patients with dual diagnoses and patients without comorbidity represent different subgroups should be strongly considered; it forms the basis for differential treatment modalities aimed at such subgroups. Our data, interestingly, show the possibility of even more complex patterns of comorbidity. For example, of 65 adolescents admitted to our drug and alcohol treatment program, 13 (20.0%) had substance abuse diagnoses in addition to diagnoses of both major depression and conduct disorder; 18 (27.7%) had comorbid substance abuse and major depression without conduct disorder. Obviously, prospective and longitudinal studies, as Dr. Calache suggests, will be critical in establishing the importance of diagnostic subgroups based on comorbidity.

OSCAR G. BUKSTEIN, M.D., M.P.H.  
DAVID A. BRENT, M.D.  
YIFRAH KAMINER, M.D.  
*Pittsburgh, Pa.*

## Ensuring the Normalcy of "Normal" Volunteers

SIR: Uriel Halbreich, M.D., and associates (1) recently reported that 16.5% of their 121 self-proclaimed "normal" research volunteers, despite preliminary telephone screening, met the Research Diagnostic Criteria for current mental health disorders when they received structured diagnostic assessment with the Schedule for Affective Disorders and Schizophrenia (SADS) interview. We would like to give a brief report on our own data from the clinical research program of the Department of Psychiatry at the Emory University School of Medicine.

Volunteers were recruited by newspaper advertisements and by referrals from other volunteers who had participated in the program. They were initially screened by telephone by experienced research clinicians. Volunteers were questioned in detail about any current or previous episodes of mental illness and any abuse of alcohol or use of street or prescription medications. If a volunteer gave an affirmative answer to any question about possible mental health problems, including drug and alcohol abuse, then he or she also received an abridged, structured telephone interview that incorporated many of the key questions from the SADS interview. If the volunteer again responded positively to questions about present or previous mental health disorders or substance abuse, he or she was not considered further as a possible participant in our normal volunteer program and is not included in the data presented here. All volunteers were told that, as part of their evaluation, they would have to provide urine specimens for toxicology screens for alcohol and prescription and street drugs and that they could not be used as research subjects if their urine toxicology screens were positive for any substance.

After the telephone screening, 103 subjects received SADS interviews with trained and experienced clinicians and had urine toxicology screens as part of a much more comprehensive medical and diagnostic evaluation. Seventy-seven (74.8%) of the volunteers were normal according to the RDC and had negative urine toxicology screens. Four subjects (3.9%) met the RDC for past episodes of major depressive disorder, and one (0.97%) met the RDC for antisocial personality. Thus, only five (4.9%) of our telephone-screened volunteers met the RDC for

an axis I psychiatric diagnosis. However, 21 (27.6%) of the first 76 volunteers had urine toxicology screens positive for drugs of abuse, including cannabis, cocaine, and/or barbiturates. All of these 21 subjects had denied, during their telephone screening and subsequent clinical interviews and SADS interviews, any previous history of substance abuse. Because of our experience with these subjects, when our next 27 volunteers were screened, they were told that they would not be paid for their research participation if their urine toxicology screens were positive. For these 27 subjects, none of the urine toxicology screens were positive ( $Z=3.08$ ,  $p=0.001$ ).

Our data suggest the utility of telephone screening to eliminate most volunteers with current or past psychiatric illness (excluding substance abuse or dependence). However, the data also suggest that simply indicating to volunteers that they will have urine toxicology screens and that they cannot be used as research subjects if their toxicology screens are positive is not an effective way to eliminate drug abusers. The additional statement that financial reimbursement will be withheld in cases of positive toxicology screens also appears necessary.

## REFERENCE

1. Halbreich U, Bakhai Y, Bacon KB, et al: The normalcy of self-proclaimed "normal volunteers." *Am J Psychiatry* 1989; 146: 1052-1055

S. CRAIG RISCH, M.D.  
 RICHARD J. LEWINE, PH.D.  
 RITA D. JEWART, PH.D.  
 MARY B. ECCARD, R.N., M.S.  
 J. STEPHEN MCDANIEL, M.D.  
 EMILE D. RISBY, M.D.  
*Atlanta, Ga.*

## Dr. Halbreich Replies

SIR: Dr. Risch and associates' report of their experience of screening volunteers for participation in studies of normal behavior underscores the necessity for in-depth, detailed assessment of these volunteers. Their report is basically in agreement with ours, as well as with Coryell and Zimmerman's finding (1) that volunteers' claims of normalcy (whatever that means) cannot be taken for granted. Their current status and past histories should be scrutinized in the same careful way as those of patients. Whether this detailed screening can be done in a phone interview or should be delayed for a face-to-face interview still needs to be clarified.

There are also some ethical issues involved. Not every institutional review board for human subjects would approve an in-depth telephone interview, and if it is approved, a verbal, structured, and documented consent is required. Withholding financial reimbursement on the basis of quality of results is another critical issue that would not be accepted by some review boards, even though I personally believe that Dr. Risch and associates' approach is right.

I wish that Dr. Risch and his colleagues would also report on the family histories of their healthy control subjects, because several biological variables have been reported to differ between healthy subjects with family histories of various mental disorders and those without such family histories (1—

3, and unpublished paper by S. Goldstein and U. Halbreich, 1989). Nevertheless, their letter supports the notion that in every report comparing a target patient group with healthy control subjects, the screening procedures and detailed characteristics of the control subjects should be described.

## REFERENCES

1. Coryell W, Zimmerman M: HPA-axis abnormalities in psychiatrically well controls. *Psychiatry Res* 1987; 20:265-273
2. Schuckit MA: Subjective response to alcohol in sons of alcoholics and control subjects. *Arch Gen Psychiatry* 1984; 41:879-884
3. Wiesel F, Fyro B, Nyback H, et al: Relationships in healthy volunteers between secretion of monoamine metabolites in urine and family history of psychiatric morbidity. *Biol Psychiatry* 1982; 17:1403-1413

URIEL HALBREICH, M.D.  
*Buffalo, N.Y.*

## Criticism of Review of Book on Divorce

SIR: I am writing to express my irritation at the book review by John W. Jacobs, M.D., of *Divorce as a Developmental Process* in the September 1989 issue of the *Journal* (1).

Although I have not read the book, I am disturbed by the profound and simplistic assumptions about "feminism" expressed in the review. Dr. Jacobs writes that a "feminist perspective" will cast men as "villains" (p. 1224). The review implies that feminists have a pathological dislike of men and that feminist therapists will be biased in favor of women.

Dr. Jacobs then states that a "less stringent feminist position . . . supports adult development of both sexes" (p. 1224). Is this the homeopathic prescription for the disease of feminism?

As most psychiatrists are aware, feminism is an evolving theory or group of theories of gender analysis widely published in sociological, historical, and anthropological literature. Many people, even therapists, describe themselves as feminists—with, of course, different understandings of the term. Obviously, the term "feminism" has acquired interesting and varied symbolic meanings.

As a nonpsychiatrist, I hope that any therapist would want to explore the personalized interpretations or pronouncements of "feminism" by any client. Unfortunately, clients are not in a similar advantageous position to explore the understandings of their therapists.

Sometimes it's a little scary out here for us nonpsychiatrist readers when we realize that psychiatrists are the ones defining feminism as essentially pathological. After all, psychiatrists get to write the *Diagnostic and Statistical Manual of Mental Disorders*.

## REFERENCE

1. Jacobs JW: Book review, JH Gold (ed): *Divorce as a Developmental Process*. *Am J Psychiatry* 1989; 146:1223-1224

KATHLEEN MURPHY MALLINGER, PH.D.  
*San Diego, Calif.*

## Dr. Jacobs Replies

SIR: Dr. Mallinger states that I wrote that a "feminist perspective" will cast men as "villains." After careful scrutiny I believe I said no such thing. Furthermore, since Dr. Mallinger puts quotation marks around "feminist perspective" and "villains" only, I must assume that she herself understands that I did not say it. What I did say is, "Judith Gold once again returns to the central theme of the book—*her* feminist perspective on the effect of divorce on women. Although men are mentioned, they are usually cast as villains" (*italics added*). Clearly, I was saying that this appears to be Dr. Gold's personal view. I cannot understand how Dr. Mallinger could so severely misinterpret my meaning. Having thus set me up, she then goes on to label my request for more evenhanded awareness of gender-specific issues and problems of divorcing couples as a "homeopathic prescription." I call it good psychotherapy.

Dr. Mallinger seems to be using my book review to make

a political statement about feminism and psychiatry. If I am correctly reading between the lines, she is not only accusing me of a lack of sensitivity to the issues but expressing similar concerns about the entire psychiatric profession. I share her concern that psychiatrists be educated about and aware of gender issues in the theory and practice of psychotherapy, and I thought I made that amply clear. Perhaps she should not criticize a book review without reading the book and understanding the review's context.

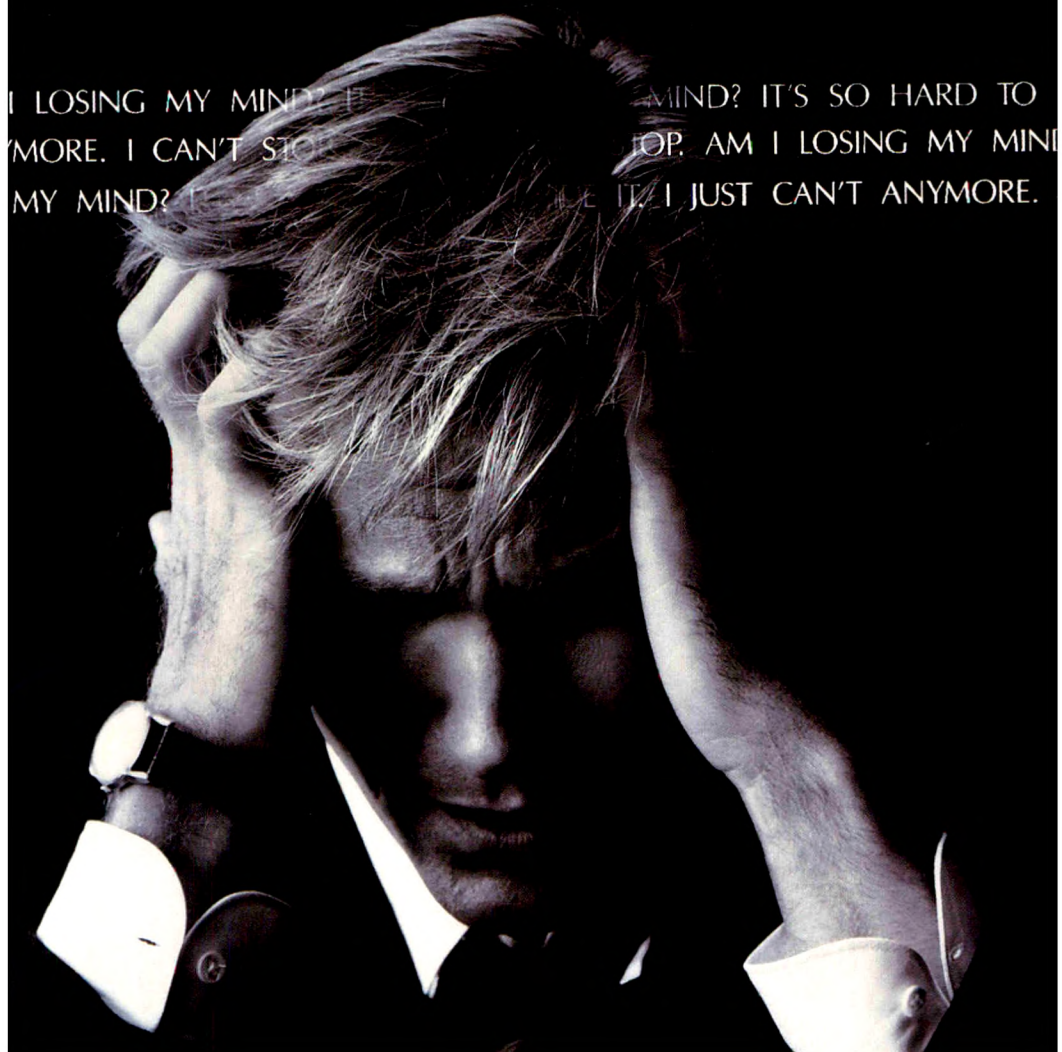
Dr. Mallinger truly is getting carried away with her subject and is being absurd when she suggests that my review in any way defines "feminism as essentially pathological." Finally, let me assure her that I have had nothing to do with the writing of the *Diagnostic and Statistical Manual*, and concerns about that or the manual's use should be addressed to another person.

JOHN W. JACOBS, M.D.  
New York, N.Y.

*Reprints of letters to the Editor are not available.*

# NEW

## Powerful medicine stop intrusive thoughts and acts









INTRODUCING

**N E W**

# **Anafranil**<sup>®</sup>

clomipramine HCl

**Powerful tricyclic therapy for  
obsessive-compulsive disorder**

- ▲ *Relieves obsessions and compulsions in OCD patients with or without concomitant depression*

***Reduces anxiety-producing intrusive thoughts<sup>1</sup>***

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***Reduces ritualized behavior<sup>1</sup>***

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- ▲ *Dual mode of action creates a unique treatment role*

*Anafranil is believed to block the reuptake of serotonin and norepinephrine.<sup>2,3</sup>*

- ▲ *Safety and tolerability demonstrated in over 20 years of worldwide use*

***Symptoms are substantially reduced in approximately 58% of patients.<sup>4</sup>***

*The most common adverse events are dry mouth, somnolence, tremor, dizziness, constipation, and ejaculatory failure. Anafranil may lower the seizure threshold. See warnings and full Prescribing Information on the following pages.*

**References:** 1. DeVeaugh-Geiss J, Landau P, Katz R. Treatment of obsessive-compulsive disorder with clomipramine. *Psychiatr Ann.* 1989;19:97-101. 2. Insel TR, Murphy DL, Cohen RM et al. Obsessive-compulsive disorder: A double-blind trial of clomipramine and clorgyline. *Arch Gen Psychiatry.* 1983;40:605-611. 3. Zohar J, Insel TR, Zohar-Kadouch RC et al. Serotonergic responsivity in obsessive-compulsive disorder. *Arch Gen Psychiatry.* 1988;45:167-171. 4. Data on file, CIBA-GEIGY Corporation.

**CIBA-GEIGY**

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# Anafranil®

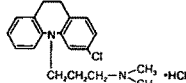
## clomipramine hydrochloride

### Capsules

#### Prescribing Information

##### DESCRIPTION

Anafranil, clomipramine hydrochloride, is an antidepressant drug that belongs to the class (dibenzazepine) of pharmacologic agents known as tricyclic antidepressants. Anafranil is available as capsules of 25, 50, and 75 mg for oral administration. Clomipramine hydrochloride is 3-chloro-5-[3-(dimethylamino)propyl]-10,11-dihydro-5H-dibenz[b,f]azepine monohydrochloride, and its structural formula is:



Clomipramine hydrochloride is a white to off-white crystalline powder. It is freely soluble in water, in methanol, and in methylene chloride, and insoluble in ethyl ether and in hexane. Its molecular weight is 351.3.

**Inactive Ingredients:** D&C Red No. 33 (25-mg capsules only), D&C Yellow No. 10, FD&C Blue No. 1 (50-mg capsules only), FD&C Yellow No. 6, gelatin, magnesium stearate, methylparaben, propylparaben, silicon dioxide, sodium lauryl sulfate, starch, and titanium dioxide.

##### CLINICAL PHARMACOLOGY

###### Pharmacodynamics

Clomipramine (CMI) is presumed to influence obsessive and compulsive behaviors through its effects on serotonergic neuronal transmission. The actual neurochemical mechanism is unknown, but CMI's relatively selective capacity to inhibit the reuptake of serotonin (5-HT) as compared to norepinephrine (NE) may be important.

###### Pharmacokinetics

**Absorption/Bioavailability:** CMI from Anafranil capsules is as bioavailable as CMI from a solution. The bioavailability of CMI from capsules is not significantly affected by food.

In a dose proportionality study involving multiple CMI doses, steady-state plasma concentrations ( $C_{ss}$ ) and area-under-plasma-concentration-time curves (AUC) of CMI and CMI's major active metabolite, desmethylclomipramine (DMI), were not proportional to dose over the ranges evaluated, i.e., between 25-100 mg/day and between 25-150 mg/day, although  $C_{ss}$  and AUC are approximately linearly related to dose between 100-150 mg/day. The relationship between dose and CMI/DMI concentrations at higher daily doses has not been systematically assessed, but if there is significant dose dependency at doses above 150 mg/day, there is the potential for dramatically higher  $C_{ss}$  and AUC even for patients dosed within the recommended range. This may pose a potential risk to some patients (see WARNINGS and PRECAUTIONS, Drug Interactions).

After a single 50-mg oral dose, maximum plasma concentrations of CMI occur within 2-6 hours (mean, 4.7 hr) and range from 56 ng/ml to 154 ng/ml (mean, 92 ng/ml). After multiple daily doses of 150 mg of Anafranil, steady-state maximum plasma concentrations range from 94 ng/ml to 339 ng/ml (mean, 218 ng/ml) for CMI and from 134 ng/ml to 532 ng/ml (mean, 274 ng/ml) for DMI. No pharmacokinetic information is available for doses ranging from 150 mg/day to 250 mg/day, the maximum recommended daily dose.

**Distribution:** CMI distributes into cerebrospinal fluid (CSF) and brain and into breast milk. DMI also distributes into CSF, with a mean CSF/plasma ratio of 2.6. The protein binding of CMI is approximately 97%, principally to albumin, and is independent of CMI concentration. The interaction between CMI and other highly protein-bound drugs has not been fully evaluated, but may be important (see PRECAUTIONS, Drug Interactions).

**Metabolism:** CMI is extensively biotransformed to DMI and other metabolites and their glucuronide conjugates. DMI is pharmacologically active, but its effects on OCD behaviors are unknown. These metabolites are excreted in urine and feces, following biliary elimination. After a 25-mg radiolabeled dose of CMI in two subjects, 60% and 51%, respectively, of the dose were recovered in the urine and 32% and 24%, respectively, in the feces. In the same study, the combined urinary recoveries of CMI and DMI were only about 0.9-1.3% of the dose administered. CMI does not induce drug-metabolizing enzymes, as measured by antipyrine half-life.

**Elimination:** Evidence that the  $C_{ss}$  and AUC for CMI and DMI may increase disproportionately with increasing oral dose suggests that the metabolism of CMI and DMI may be capacity limited. This fact must be considered in assessing the estimates of the pharmacokinetic parameters presented below, as these were obtained in individuals exposed to doses of 150 mg. If the pharmacokinetics of CMI and DMI are nonlinear at doses above 150 mg, their elimination half-lives may be considerably lengthened at doses near the upper end of the recommended dosing range (i.e., 200 mg/day to 250 mg/day). Consequently, CMI and DMI may accumulate, and this accumulation may increase the incidence of any dose- or plasma-concentration-dependent adverse reactions, in particular seizures (see WARNINGS).

After a 150-mg dose, the half-life of CMI ranges from 19 hours to 37 hours (mean, 32 hr) and that of DMI ranges from 54 hours to 77 hours (mean, 69 hr). Steady-state levels after multiple dosing are typically reached within 7-14 days for CMI. Plasma concentrations of the metabolite exceed the parent drug on multiple dosing. After multiple dosing with 150 mg/day, the accumulation factor for CMI is approximately 2.5 and for DMI is 4.6. Importantly, it may take two weeks or longer to achieve this extent of accumulation at constant dosing because of the relatively long elimination half-lives of CMI and DMI (see DOSAGE AND ADMINISTRATION). The effects of hepatic and renal impairment on the disposition of Anafranil have not been determined.

**Pharmacokinetic Interactions:** Coadministration of haloperidol with CMI increases plasma concentrations of CMI. Coadministration of CMI with phenobarbital increases plasma concentrations of phenobarbital (see PRECAUTIONS, Drug Interactions). Younger subjects (18-40 years of age) tolerated CMI better and had significantly lower steady-state plasma concentrations, compared with subjects over 65 years of age. Children under 15 years of age had significantly lower plasma concentration/dose ratios, compared with adults. Plasma concentrations of CMI were significantly higher in smokers than in nonsmokers.

##### INDICATIONS AND USAGE

Anafranil is indicated for the treatment of obsessions and compulsions in patients with Obsessive-Compulsive Disorder (OCD). The obsessions or compulsions must cause marked distress, be time-consuming, or significantly interfere with social or occupational functioning, in order to meet the DSM-III-R (circa 1989) diagnosis of OCD.

Obsessions are recurrent, persistent ideas, thoughts, images, or impulses that are ego-dystonic. Compulsions are repetitive, purposeful, and intentional behaviors performed in response to an obsession or in a stereotyped fashion, and are recognized by the person as excessive or unreasonable.

The effectiveness of Anafranil for the treatment of OCD was demonstrated in multicenter, placebo-controlled, parallel-group studies, including two 10-week studies in adults and one 8-week study in children and adolescents 10-17 years of age. Patients in all studies had moderate-to-severe OCD (DSM-III), with mean baseline ratings on the Yale-Brown Obsessive Compulsive Scale (YBOCS) ranging from 26 to 28 and a mean baseline rating of 10 on the NIMH Clinical Global Obsessive Compulsive Scale (NIMH-OCS). Patients taking CMI experienced a mean reduction of approximately 10 on the YBOCS, representing an average improvement on this scale of 35% to 42% among adults and 37% among children and adolescents. CMI-treated patients experienced a 3.5 unit decrement on the NIMH-OCS. Patients on placebo showed no important clinical response on either scale. The maximum dose was 250 mg/day for most adults and 3 mg/kg/day (up to 200 mg) for all children and adolescents.

The effectiveness of Anafranil for long-term use (i.e., for more than 10 weeks) has not been systematically evaluated in placebo-controlled trials. The physician who elects to use Anafranil for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

##### CONTRAINDICATIONS

Anafranil is contraindicated in patients with a history of hypersensitivity to Anafranil or other tricyclic antidepressants.

Anafranil should not be given in combination, or within 14 days of treatment, with a monoamine oxidase (MAO) inhibitor. Hyperpyretic crisis, seizures, coma, and death have been reported in patients receiving such combinations.

Anafranil is contraindicated during the acute recovery period after a myocardial infarction.

##### WARNINGS

###### Seizures

During premarket evaluation, seizure was identified as the most significant risk of Anafranil use.

The observed cumulative incidence of seizures among patients exposed to Anafranil at doses up to 300 mg/day was 0.64% at 90 days, 1.12% at 180 days, and 1.45% at 365 days. The cumulative rates cited correct the crude rate (i.e., 0.7%, 25/3519) for the variable duration of exposure times among the patients who participated in the development program.

Although dose appears to be a predictor of seizure, there is a confounding of dose and duration of exposure, making it difficult to assess independently the effect of either factor alone. The ability to predict the occurrence of seizures in subjects exposed to doses of CMI greater than 250 mg is limited, given that the plasma concentration of CMI may be dose-dependent and may vary among subjects given the same dose. Nevertheless, prescribers are advised to limit the daily dose to a maximum of 250 mg in adults and 3 mg/kg (or 200 mg) in children and adolescents (see DOSAGE AND ADMINISTRATION).

Rare reports of fatalities in association with seizures have been recorded by foreign post-marketing surveillance systems over the 20 years of Anafranil's non-domestic marketing. In some of these cases, Anafranil had been administered by other epileptogenic agents; in others, the patients involved had possibly predisposing medical conditions.

Caution should be used in administering Anafranil to patients with a history of seizures or other predisposing factors, e.g., brain damage of varying etiology, alcoholism, and concomitant use with other drugs that lower the seizure threshold.

Physicians should discuss with patients the risk of taking Anafranil while engaging in activities in which sudden loss of consciousness could result in serious injury to the patient or others, e.g., the operation of complex machinery, driving, swimming, climbing.

###### PRECAUTIONS

###### General

**Suicide:** Since depression is a commonly associated feature of OCD, the risk of suicide must be considered. Prescriptions for Anafranil should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

**Cardiovascular Effects:** Modest orthostatic decreases in blood pressure and modest tachycardia were each seen in approximately 20% of patients taking Anafranil in clinical trials; but patients were frequently asymptomatic. Among approximately 1400 patients treated with CMI in the premarketing experience who had ECGs, 1.5% developed abnormalities during treatment, compared with 3.1% of patients receiving active control drugs and 0.7% of patients receiving placebo. The most common ECG changes were PVCs, ST-T wave changes, and intraventricular conduction abnormalities. These changes were rarely associated with significant clinical symptoms. Nevertheless, caution is necessary in treating patients with known cardiovascular disease, and gradual dose titration is recommended.

**Psychosis, Confusion, And Other Neuropsychiatric Phenomena:** Patients treated with Anafranil have been reported to show a variety of neuropsychiatric signs and symptoms including delusions, hallucinations, psychotic episodes, confusion, and paranoia. Because of the uncontrolled nature of many of the studies, it is impossible to provide a precise estimate of the extent of risk imposed by treatment with Anafranil. As with tricyclic antidepressants to which it is closely related, Anafranil may precipitate an acute psychotic episode in patients with unrecognized schizophrenia.

**Mania/Hypomania:** During premarketing testing of Anafranil in patients with affective disorder, hypomania or mania was precipitated in several patients. Activation of mania or hypomania has also been reported in a small proportion of patients with affective disorder treated with marketed tricyclic antidepressants, which are closely related to Anafranil.

**Hepatic Changes:** During premarketing testing, Anafranil was occasionally associated with elevations in SGOT and SGPT (pooled incidence of approximately 1% and 3%, respectively) of potential clinical importance (i.e., values greater than 3 times the upper limit of normal). In the vast majority of instances these enzyme increases were not associated with other clinical findings suggestive of hepatic injury; moreover, none were jaundiced. Rare reports of more severe liver injury, some fatal, have been recorded in foreign post-marketing experience. Caution is indicated in treating patients with known liver disease, and periodic monitoring of hepatic enzyme levels is recommended in such patients.

**Hematologic Changes:** Although no instances of severe hematologic toxicity were seen in the premarketing experience with Anafranil, there have been post-marketing reports of leukopenia, agranulocytosis, thrombocytopenia, anemia, and pancytopenia in association with Anafranil use. As is the case with tricyclic antidepressants to which Anafranil is closely related, leukocyte and differential blood counts should be obtained in patients who develop fever and sore throat during treatment with Anafranil.

**Central Nervous System:** More than 30 cases of hyperthermia have been recorded by non-domestic post-marketing surveillance systems. Most cases occurred when Anafranil was used in combination with other drugs when Anafranil and a neuroleptic were used concomitantly, the cases were sometimes considered to be examples of a neuroleptic malignant syndrome.

**Sexual Dysfunction:** The rate of sexual dysfunction in male patients with OCD who were treated with Anafranil in the premarketing experience was markedly increased compared with placebo controls (i.e., 42% experienced ejaculation failure and 20% experienced impotence, compared with 2.0% and 2.6%, respectively, in the placebo group). Approximately 85% of males with sexual dysfunction chose to continue treatment. **Weight Changes:** In controlled studies of OCD, weight gain was reported in 18% of patients receiving Anafranil, compared with 1% of patients receiving placebo. In these studies, 28% of patients receiving Anafranil had a weight gain of at least 7% of their initial body weight, compared with 4% of patients receiving placebo. Several patients had weight gains in excess of 25% of their initial body weight. Conversely, 5% of patients receiving Anafranil and 1% receiving placebo had weight losses of at least 7% of their initial body weight.

**Electroconvulsive Therapy:** As with closely related tricyclic antidepressants, concurrent administration of Anafranil with electroconvulsive therapy may increase the risks; such treatment should be limited to those patients for whom it is essential, since there is limited clinical experience.

**Surgery:** Prior to elective surgery with general anesthetics, therapy with Anafranil should be discontinued for as long as is clinically feasible, and the anesthetic should be adjusted.

**Use in Concomitant Illness:** As with closely related tricyclic antidepressants, Anafranil should be used with caution in the following:

1. Hypertrophic patients or patients receiving thyroid medication, because of the possibility of cardiac toxicity.
2. Patients with increased intraocular pressure, a history of narrow-angle glaucoma, or urinary retention, because of the anticholinergic properties of the drug.
3. Patients with tumors of the adrenal medulla (e.g., pheochromocytoma, neuroblastoma) in whom the drug may provoke hypertensive crises.
4. Patients with significantly impaired renal function.

**Withdrawal Symptoms:** A variety of withdrawal symptoms have been reported in association with abrupt discontinuation of Anafranil, including dizziness, nausea, vomiting, headache, malaise, sleep disturbance, hyperthermia, and irritability. In addition, such patients may experience a worsening of psychiatric status. While the withdrawal effects of Anafranil have not been systematically evaluated in controlled trials, they are well known with closely related tricyclic antidepressants, and it is recommended that the dosage be tapered gradually and the patient monitored carefully during discontinuation (see DRUG ABUSE AND DEPENDENCE).

###### Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe Anafranil:

1. The risk of seizure (see WARNINGS).
2. The relatively high incidence of sexual dysfunction among males (see PRECAUTIONS, Sexual Dysfunction).
3. Since Anafranil may impair the mental and/or physical abilities required for the performance of complex tasks, and since Anafranil is associated with a risk of seizures, patients should be cautioned about the performance of complex and hazardous tasks (see WARNINGS).
4. Patients should be cautioned about using alcohol, barbiturates, or other CNS depressants concurrently, since Anafranil may exaggerate their response to these drugs.
5. Patients should notify their physician if they become pregnant or intend to become pregnant during therapy.
6. Patients should notify their physician if they are breast-feeding.

###### Drug Interactions

The risks of using Anafranil in combination with other drugs have not been systematically evaluated. Given the primary CNS effects of Anafranil, caution is advised in using it concomitantly with other CNS-active drugs (see PRECAUTIONS, Information for Patients). Anafranil should not be used with MAO inhibitors (see CONTRAINDICATIONS).

Close supervision and careful adjustment of dosage are required when Anafranil is administered with anticholinergic or sympathomimetic drugs.

Several tricyclic antidepressants have been reported to block the pharmacologic effects of guanethidine, clonidine, or similar agents, and such an effect may be anticipated with CMI because of its structural similarity to other tricyclic antidepressants.

The plasma concentration of CMI has been reported to be increased by the concomitant administration of haloperidol; plasma levels of several closely related tricyclic antidepressants have been reported to be increased by the concomitant administration of either methyphenidate, cimetidine, or fluoxetine and such an effect may be anticipated with CMI as well. Administration of CMI has been reported to increase the plasma levels of phenobarbital, if given concomitantly (see CLINICAL PHARMACOLOGY, Pharmacokinetic Interactions).

Because Anafranil is highly bound to serum protein, the administration of Anafranil to patients taking other drugs that are highly bound to protein (e.g., warfarin, digoxin) may cause an increase in plasma concentrations of these drugs, potentially resulting in adverse effects. Conversely, adverse effects may result from displacement of protein-bound Anafranil by other highly bound drugs (see CLINICAL PHARMACOLOGY, Distribution).

###### Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year bioassay, no clear evidence of carcinogenicity was found in rats given doses 20 times the maximum daily human dose. Three out of 235 treated rats had a rare tumor (hemangioendothelioma); it is unknown if these neoplasms are compound related.

In reproduction studies, no effects on fertility were found in rats given doses approximately 5 times the maximum daily human dose.

###### Pregnancy Category C

No teratogenic effects were observed in studies performed in rats and mice at doses up to 20 times the maximum daily human dose. Slight nonspecific fetotoxic effects were seen in the offspring of pregnant mice given doses 10 times the maximum daily human dose. Slight nonspecific embryotoxicity was observed in rats given doses 5-10 times the maximum daily human dose.

There are no adequate or well-controlled studies in pregnant women.

Withdrawal symptoms, including jitteriness, tremor, and seizures, have been reported in neonates whose mothers had taken Anafranil until delivery. Anafranil should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

###### Nursing Mothers

Anafranil has been found in human milk. Because of the potential for adverse reactions, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

###### Pediatric Use

In a controlled clinical trial in children and adolescents (10-17 years of age), 46 outpatients received Anafranil for up to 8 weeks. In addition, 150 adolescent patients have received Anafranil in open-label protocols for periods of several months to several years. Of the 196 adolescents studied, 50 were 13 years of age or less and 146 were 14-17 years of age. While the adverse reaction profile in this age group (see ADVERSE REACTIONS) is similar to that in adults, it is unknown what, if any, effects long-term treatment with Anafranil may have on the growth and development of children.

The safety and effectiveness in children below the age of 10 have not been established. Therefore, specific recommendations cannot be made for the use of Anafranil in children under the age of 10.

###### Use in Elderly

Anafranil has not been systematically studied in older patients; but 152 patients at least 60 years of age participating in U.S. clinical trials received Anafranil for periods of several months to several years. No unusual age-related adverse events have been identified in this elderly population, but these data are insufficient to rule out possible age-related differences, particularly in elderly patients who have concomitant systemic illnesses or who are receiving other drugs concomitantly.

###### ADVERSE REACTIONS

###### Commonly Observed

The most commonly observed adverse events associated with the use of Anafranil and not seen at an equivalent incidence among placebo-treated patients were gastrointestinal complaints, including dry mouth, constipation, nausea, dyspepsia, and anorexia; nervous system complaints, including somnolence, tremor, dizziness, nervousness, and myoclonus; genitourinary complaints, including changed libido, ejaculatory failure, impotence, and micturition disorder; and other miscellaneous complaints, including fatigue, sweating, increased appetite, weight gain, and visual changes.

###### Leading to Discontinuation of Treatment

Approximately 20% of 3916 patients who received Anafranil in U.S. premarketing clinical trials discontinued treatment because of an adverse event. Approximately one-half of the patients who discontinued (8% of the total) had multiple complaints, none of which could be classified as primary. Where a primary reason for discontinuation could be identified, most patients discontinued because of nervous system complaints (5.4%), primarily somnolence. The second-most frequent reason for discontinuation was digestive system complaints (1.3%), primarily vomiting and nausea.

###### Incidence in Controlled Clinical Trials

The following table enumerates adverse events that occurred at an incidence of 1% or greater among patients with OCD who received Anafranil in adult or pediatric placebo-controlled clinical trials. The frequencies were obtained from pooled data of clinical trials involving either adults receiving Anafranil (N = 322) or placebo (N = 319) or children treated with Anafranil (N = 46) or placebo (N = 44). The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice, in which patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, provide the physician with a basis for estimating the relative contribution of drug and nondrug factors to the incidence of side effects in the populations studied.

Incidence of Treatment-Emergent Adverse Experience in Placebo-Controlled Clinical Trials (Percentage of Patients Reporting)

Body System/ Adverse Event*	Adults		Children and Adolescents	
	Anafranil (N=322)	Placebo (N=319)	Anafranil (N=46)	Placebo (N=44)
Nervous System				
Somnolence	54	16	46	11
Tremor	54	2	33	2
Dizziness	54	14	41	14
Headache	52	41	28	34
Insomnia	25	15	11	7

## Anafanil\* clomipramine hydrochloride

Body System/ Adverse Event*	Adults		Children and Adolescents	
	Anafanil (N=322)	Placebo (N=319)	Anafanil (N=46)	Placebo (N=44)
Urbid change	21	3	—	—
Nervousness	18	—	—	—
Myoclonus	13	—	4	2
Increased appetite	11	2	—	2
Paresthesia	9	3	2	2
Memory impairment	9	1	7	2
Anxiety	9	4	—	—
Twitching	7	1	4	5
Impaired concentration	5	2	—	—
Depression	5	1	—	—
Hypertonia	4	1	2	—
Sleep disorder	4	—	9	5
Psychosomatic disorder	3	—	—	—
Yawning	3	—	—	—
Confusion	3	—	2	—
Speech disorder	3	—	—	—
Abnormal dreaming	3	—	—	2
Agitation	3	—	—	—
Migraine	3	—	—	—
Depersonalization	2	—	2	—
Irritability	2	2	2	—
Emotional lability	2	—	—	2
Panic reaction	1	—	2	—
Aggressive reaction	—	—	—	—
Paresis	—	—	2	—
<b>Skin and Appendages</b>				
Increased sweating	29	3	9	—
Rash	8	1	4	2
Pruritus	8	—	2	—
Dermatitis	2	—	—	2
Acne	2	2	—	5
Dry skin	2	—	—	—
Urticaria	1	—	—	—
Abnormal skin odor	—	—	2	—
<b>Digestive System</b>				
Dry mouth	84	17	63	16
Constipation	47	11	22	9
Nausea	33	14	9	11
Dyspepsia	22	10	13	2
Diarrhea	13	9	7	5
Anorexia	12	—	22	2
Abdominal pain	11	9	13	16
Vomiting	7	2	7	—
Flatulence	6	—	—	2
Tooth disorder	5	—	—	2
Gastrointestinal disorder	5	—	—	—
Dysphagia	2	—	—	—
Esophagitis	1	—	—	—
Eruetion	—	—	2	2
Ulcerative stomatitis	—	—	2	—
<b>Body as a Whole</b>				
Fatigue	39	18	35	9
Weight increase	18	1	2	—
Flushing	8	—	7	—
Hot flushes	5	—	2	—
Chest pain	4	4	7	—
Fever	4	—	7	7
Allergy	3	3	2	5
Pain	3	2	4	2
Local edema	2	4	—	—
Chills	2	1	—	—
Weight decrease	—	—	7	—
Otitis media	—	—	4	5
Asthenia	—	—	2	—
Haltosis	—	—	2	—
<b>Cardiovascular System</b>				
Postural hypotension	6	—	4	—
Palpitation	4	2	4	—
Tachycardia	4	—	2	—
Syncope	—	—	2	—
<b>Respiratory System</b>				
Pharyngitis	14	9	—	5
Rhinitis	12	10	7	9
Sinusitis	6	4	2	5
Coughing	6	6	4	5
Bronchospasm	2	—	7	2
Epistaxis	2	—	2	—
Dyspnea	2	—	—	—
Laryngitis	—	1	2	—
<b>Urogenital System</b>				
<b>Male and Female Patients Combined</b>				
Micturition disorder	14	2	4	2
Urinary tract infection	6	1	—	—
Micturition frequency	5	3	—	—
Urinary retention	—	—	7	—
Dysuria	2	2	—	—
Cystitis	2	—	—	—
<b>Female Patients Only</b>	(N=172)	(N=167)	(N=10)	(N=21)
Dysmenorrhea	12	14	10	10
Lactation (nonpuerperal)	4	—	—	—
Menstrual disorder	4	2	—	—
Vaginitis	2	—	—	—
Leukorrhea	2	—	—	—
Breast enlargement	2	—	—	—
Breast pain	1	—	—	—
Amenorrhea	1	—	—	—
<b>Male Patients Only</b>	(N=140)	(N=152)	(N=36)	(N=23)
Ejaculation failure	42	2	6	—
Impotence	20	3	—	—
<b>Special Senses</b>				
Abnormal vision	18	4	7	2
Taste perversion	8	—	4	—
Tinnitus	6	—	4	—
Abnormal lacrimation	3	2	—	—
Mydriasis	2	—	—	—
Conjunctivitis	1	—	—	—
Anisocoria	—	—	2	—
Blepharospasm	—	—	2	—
Ocular allergy	—	—	—	—
Vestibular disorder	—	—	2	2
<b>Musculoskeletal</b>				
Myalgia	13	9	—	—
Back pain	6	6	—	—
Arthralgia	3	5	—	—
Muscle weakness	1	—	2	—
<b>Hemic and Lymphatic</b>				
Purpura	3	—	—	—
Anemia	—	—	2	2
<b>Metabolic and Nutritional</b>				
Thirst	2	2	—	2

## Other Events Observed During the Premarketing Evaluation of Anafanil

During clinical testing in the U.S., multiple doses of Anafanil were administered to approximately 3800 subjects. Unwanted events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of unwanted events into a smaller number of standardized event categories.

In the tabulations that follow, a modified World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the 3525 individuals exposed to Anafanil who experienced an event of the type cited on at least one occasion while receiving Anafanil. All events are included except those already listed in the previous table, those reported in terms so general as to be uninformative, and those in which an association with the drug was remote. It is important to emphasize that although the events reported occurred during treatment with Anafanil, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in less than 1/1000 patients.

**Body as a Whole:** Infrequent — general edema, increased susceptibility to infection, malaise. Rare — dependent edema, withdrawal syndrome. **Cardiovascular System:** Infrequent — abnormal ECG, arrhythmia, bradycardia, cardiac arrest, extrasystoles, palpitations, aneurysm, atrial flutter, bundle branch block, cardiac failure, cerebral hemorrhage, heart block, myocardial infarction, myocardial ischemia, peripheral ischemia, thrombophlebitis, vasospasm, ventricular tachycardia.

**Digestive System:** Infrequent — abnormal hepatic function, blood in stool, colitis, duodenitis, gastric ulcer, gastritis, gastroesophageal reflux, gingivitis, glossitis, hemorrhoids, hepatitis, increased saliva, irritable bowel syndrome, peptic ulcer, rectal hemorrhage, tongue ulceration, tooth caries. Rare — cheilitis, chronic enteritis, discolored feces, gastric dilatation, gingival bleeding, hiccup, intestinal obstruction, oral/pharyngeal edema, paralytic ileus, salivary gland enlargement.

**Endocrine System:** Infrequent — hypothyroidism. Rare — goiter, gynecomastia, hyperthyroidism.

**Hemic and Lymphatic System:** Infrequent — lymphadenopathy. Rare — leukemoid reaction, lymphoma-like disorder, marrow depression.

**Metabolic and Nutritional System:** Infrequent — dehydration, diabetes mellitus, gout, hypercholesterolemia, hyperglycemia, hyperuricemia, hypokalemia. Rare — fat intolerance, glycosuria.

**Musculoskeletal System:** Infrequent — arthrosis. Rare — dystonia, exostosis, lupus erythematosus rash, bruising, myopathy, myositis, polyarthritis nodosa, torticollis.

**Nervous System:** Frequent — abnormal thinking, vertigo. Infrequent — abnormal coordination, abnormal EEG, abnormal gait, apathy, ataxia, coma, convulsions, delirium, delusion, dyskinesia, dysphonia, encephalopathy, euphoria, extrapyramidal disorder, hallucinations, hostility, hyperkinesia, hyperreflexia, hallucinations, hypokinesia, leg cramps, manic reaction, neuritis, paranoia, phobic disorder, psychosis, sensory disturbance, somnambulism, stimulation, suicidal ideation, suicide attempt, teeth-grinding. Rare — anticholinergic syndrome, aphasia, apraxia, cataplexy, cholinergic syndrome, choreoathetosis, generalized spasm, hemiparesis, hyperreflexia, hyperreflexia, hyposthesia, illusion, impaired impulse control, indecisiveness, mutism, neuropathy, nystagmus, oculogyric crisis, oculomotor nerve paralysis, schizophrenic reaction, stupor, suicide.

**Respiratory System:** Infrequent — bronchitis, hyperventilation, increased sputum, pneumonia. Rare — cyanosis, hemoptysis, hyperventilation, laryngismus.

**Skin and Appendages:** Infrequent — alopecia, cellulitis, cyst, eczema, erythematous rash, genital pruritus, maculopapular rash, photosensitivity reaction, pruritus, pustular rash, skin discoloration. Rare — chloasma, folliculitis, hypertrichosis, pterocarcinoma, seborrhea, skin hypertrophy, skin ulceration.

**Special Senses:** Infrequent — abnormal accommodation, deafness, diplopia, earache, eye pain, foreign body sensation, hyperacusis, parosmia, photophobia, scleritis, taste loss. Rare — blepharitis, chromatopsia, conjunctival hemorrhage, exophthalmos, glaucoma, keratitis, labyrinth disorder, night blindness, retinal disorder, strabismus, visual field defect.

**Urogenital System:** Infrequent — endometriosis, epididymitis, hematuria, nocturia, oliguria, ovarian cyst, perineal pain, pyuria, prostatic disorder, renal calculus, renal pain, testis disorder, urethral disorder, urinary incontinence, uterine hemorrhage, vaginal hemorrhage. Rare — albuminuria, anorgasm, breast engorgement, breast fibroadenosis, cervical dysplasia, endometrial hyperplasia, premature ejaculation, pyelonephritis, pyuria, renal cyst, uterine inflammation, vulvar disorder.

## DRUG ABUSE AND DEPENDENCE

Anafanil has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. While a variety of withdrawal symptoms have been described in association with Anafanil discontinuation (see PRECAUTIONS, Withdrawal Symptoms), there is no evidence for drug-seeking behavior, except for a single report of potential Anafanil abuse by a patient with a history of dependence on codeine, benzodiazepines, and multiple psychoactive drugs. The patient received Anafanil for depression and panic attacks and appeared to become dependent after hospital discharge.

Despite the lack of evidence suggesting an abuse liability for Anafanil in foreign marketing, it is not possible to predict the extent to which Anafanil might be misused or abused once marketed in the U.S. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely.

## OVERDOSAGE

## Human Experience

In U.S. clinical trials, 2 deaths occurred in 12 reported cases of acute overdosage with Anafanil either alone or in combination with other drugs. One death involved a patient suspected of ingesting a dose of 7000 mg. The second death involved a patient suspected of ingesting a dose of 5750 mg. The 10 nonfatal cases involved doses of up to 5000 mg, accompanied by plasma levels of up to 1010 ng/ml. All 10 patients completely recovered. Among reports from other countries of Anafanil overdosage, the lowest dose associated with a fatality was 750 mg. Based upon post-marketing reports in the United Kingdom, CMI's lethality in overdosage is considered to be similar to that reported for closely related tricyclic compounds marketed as antidepressants.

## Signs and Symptoms

Signs and symptoms vary in severity depending upon factors such as the amount of drug absorbed, the age of the patient, and the time elapsed since drug ingestion. Blood and urine levels of Anafanil may not reflect the severity of poisoning; they have chiefly a qualitative rather than quantitative value, and they are unreliable indicators in the clinical management of the patient. The first signs and symptoms of poisoning with tricyclic antidepressants are generally severe anticholinergic reactions. CNS abnormalities may include drowsiness, stupor, coma, ataxia, restlessness, agitation, delirium, severe perspiration, hyperactive reflexes, muscle rigidity, athetoid and choreiform movements, and convulsions. Cardiac abnormalities may include arrhythmia, tachycardia, ECG evidence of impaired conduction, and signs of congestive heart failure, and in very rare cases, cardiac arrest. Respiratory depression, cyanosis, hypotension, shock, vomiting, hyperpyrexia, mydriasis, oliguria or anuria, and diaphoresis may also be present.

## Treatment

The recommended treatment for tricyclic overdose may change periodically. Therefore, it is recommended that the physician contact a poison control center for current information on treatment.

Because CNS involvement, respiratory depression, and cardiac arrhythmia can occur suddenly, hospitalization and close observation are necessary, even when the amount ingested is thought to be small or the initial degree of intoxication appears slight or moderate. All patients with ECG abnormalities should have continuous cardiac monitoring for at least 72 hours and be closely observed until well after the cardiac status has returned to normal; relapses may occur after apparent recovery. The slow intravenous administration of physostigmine

salicylate has been reported to reverse the cardiovascular and CNS anticholinergic manifestations of tricyclic overdosage; however, it should not be used routinely, since it may induce seizures and cholinergic crises and there is persisting debate about its net utility.

In the alert patient, the stomach should be emptied promptly by induced emesis followed by lavage. In the obtunded patient, the airway should be secured with a cuffed endotracheal tube before beginning lavage (do not induce emesis). Lavage should be continued for 24 hours or longer, depending on the apparent severity of intoxication. Normal or half-normal saline should be used to avoid water intoxication, especially in children. Instillation of activated charcoal slurry may help reduce absorption of CMI.

External stimulation should be minimized to reduce the tendency for convulsions, and anticonvulsants may be necessary. If MAO inhibitors have been taken recently, barbiturates should not be used. Adequate respiratory exchange should be maintained, including intubation and artificial respiration, if necessary. Respiratory stimulants should not be used.

In severe hypotension or shock, the patient should be placed in an appropriate position and given a plasma expander, dopamine, or dobutamine by intravenous drip. The use of corticosteroids in shock is controversial and may be contraindicated in cases of overdosage with tricyclic antidepressants. Digita is may increase conduction abnormalities and further irritate an already sensitized myocardium. If congestive heart failure necessitates rapid digitalization, particular care must be exercised. Hyperventilation should be controlled by whatever external means are available, including ice packs and cooling sponge baths, if necessary. Hemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis have generally been reported as ineffective because of the rapid fixation of Anafanil in tissues.

## DOSAGE AND ADMINISTRATION

The treatment regimens described below are based on those used in controlled clinical trials of Anafanil in 520 adults, and 91 children and adolescents with OCD. During initial titration, Anafanil should be given in divided doses with meals to reduce gastrointestinal side effects. The goal of this initial titration phase is to minimize side effects by permitting tolerance to side effects to develop or allowing the patient time to adapt if tolerance does not develop.

Because both CMI and its active metabolite, DMI, have long elimination half-lives, the prescriber should take into consideration the fact that steady-state plasma levels may not be achieved until 2-3 weeks after dosage changes (see CLINICAL PHARMACOLOGY). Therefore, after initial titration, it may be appropriate to wait 2-3 weeks between further dosage adjustments.

## Initial Treatment/Dose Adjustment (Adults)

Treatment with Anafanil should be initiated at a dosage of 25 mg daily and gradually increased, as tolerated, to approximately 100 mg during the first 2 weeks. During initial titration, Anafanil should be given in divided doses with meals to reduce gastrointestinal side effects. Thereafter, the dosage may be increased gradually over the next several weeks, up to a maximum of 250 mg daily. After titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation.

## Initial Treatment/Dose Adjustment (Children and Adolescents)

As with adults, the starting dose is 25 mg daily and should be gradually increased (also given in divided doses with meals to reduce gastrointestinal side effects) during the first 2 weeks, as tolerated, up to a daily maximum of 3 mg/kg or 100 mg, whichever is smaller. Thereafter, the dosage may be increased gradually over the next several weeks up to a daily maximum of 3 mg/kg or 200 mg, whichever is smaller (see PRECAUTIONS, Pediatric Use). As with adults, after titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation.

## Maintenance/Continuation Treatment (Adults, Children, and Adolescents)

While there are no systematic studies that answer the question of how long to continue Anafanil, OCD is a chronic condition and it is reasonable to consider continuation for a responding patient. Although the efficacy of Anafanil after 10 weeks has not been documented in controlled trials, patients have been continued in therapy under double-blind conditions for up to 1 year without loss of benefit. However, dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for treatment. During maintenance, the total daily dose may be given once daily at bedtime.

## HOW SUPPLIED

**Capsules 25 mg** — ivory/melon yellow (imprinted ANAFANIL 25 mg)  
Bottles of 100 ..... NDC 0083-0115-30  
Unit Dose (blister pack)  
Box of 100 (strips of 10) ..... NDC 0083-0115-32  
**Capsules 50 mg** — ivory/aqua blue (imprinted ANAFANIL 50 mg)  
Bottles of 100 ..... NDC 3083-0116-30  
Unit Dose (blister pack)  
Box of 100 (strips of 10) ..... NDC 3083-0116-32  
**Capsules 75 mg** — ivory/yellow (imprinted ANAFANIL 75 mg)  
Bottles of 100 ..... NDC 0083-0117-30  
Unit Dose (blister pack)  
Box of 100 (strips of 10) ..... NDC 0083-0117-32

Do not store above 86°F (30°C). Protect from moisture.

Dispense in tight container (USP).

## ANIMAL TOXICOLOGY

Testicular and lung changes commonly associated with tricyclic compounds have been observed with Anafanil. In 1- and 2-year studies in rats, changes in the testes (atrophy, aspermatogenesis, and calcification) and drug-induced phospholipidosis in the lungs were observed at doses 4 times the maximum daily human dose. Testicular atrophy was also observed in a 1-year oral toxicity study in dogs at 10 times the maximum daily human dose.

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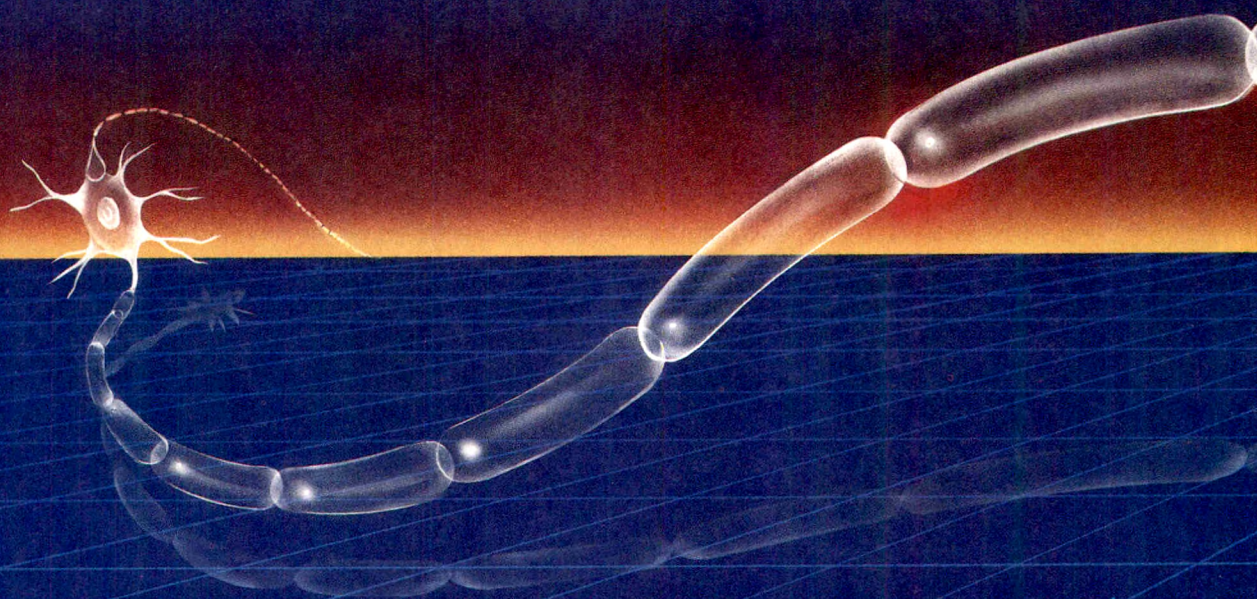
\* Events reported by at least 1% of Anafanil patients are included

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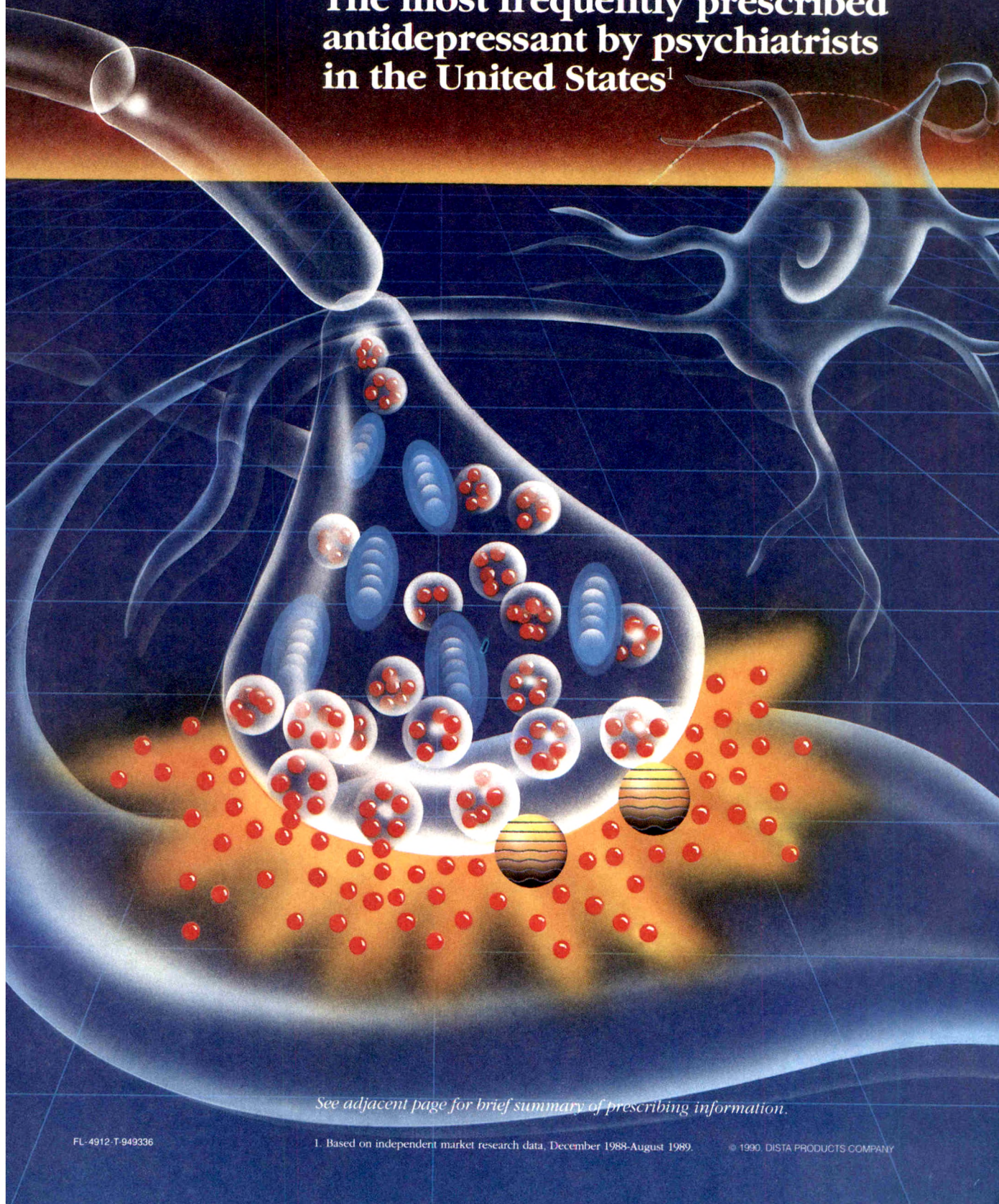
**Prozac<sup>®</sup> (fluoxetine hydrochloride)**  
**is the first highly specific,**  
**highly potent blocker**  
**of serotonin uptake**



# PROZAC<sup>®</sup>

fluoxetine hydrochloride

**The most frequently prescribed  
antidepressant by psychiatrists  
in the United States<sup>1</sup>**



*See adjacent page for brief summary of prescribing information.*



## Prozac® (fluoxetine hydrochloride)

### Brief Summary:

Consult the package literature for complete information.

**Indications:** Prozac is indicated for the treatment of depression.

**Contraindication:** Prozac is contraindicated in patients known to be hypersensitive to it.

**Warnings: Monoamine Oxidase Inhibitors**—Data on the effects of the combined use of fluoxetine and MAOI inhibitors are limited. Their combined use should be avoided. Based on experience with the combined administration of MAOIs and tricyclics, at least 14 days should elapse between discontinuation of an MAOI inhibitor and initiation of treatment with fluoxetine.

**Because of the half-life of fluoxetine and its active metabolite, at least five weeks (approximately five half-lives of norfluoxetine) should elapse between discontinuation of fluoxetine and initiation of therapy with an MAOI.** Administration of an MAOI within five weeks of discontinuation of fluoxetine may increase the risk of serious events. While a causal relationship to fluoxetine has not been established, death has been reported to occur following the initiation of MAOI therapy shortly after discontinuation of fluoxetine.

**Rash and Accompanying Events**—During premarketing testing of more than 5,600 US patients given fluoxetine, approximately 4% developed a rash and/or urticaria. Among these cases, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

Two patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but one was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was considered variously to be a vasculitis or erythema multiforme. Several other patients have had systemic syndromes suggestive of serum sickness.

Since the introduction of Prozac, systemic events, possibly related to vasculitis, have developed in patients with rash. Although these events are rare, they may be serious, involving the lung, kidney, or liver. Death has been reported to occur in association with these systemic events.

Whether these systemic events or rash have a common underlying cause or are due to different etiologies or pathogenic processes is not known. Upon the appearance of rash, Prozac should be discontinued.

**Precautions: General—Anxiety and Insomnia**—Anxiety, nervousness, and insomnia were reported by 10% to 15% of patients treated with Prozac. These symptoms led to drug discontinuation in 5% of patients treated with Prozac.

**Altered Appetite and Weight**—Significant weight loss, especially in underweight depressed patients, may be an undesirable result of treatment with Prozac.

In controlled clinical trials, approximately 9% of patients treated with Prozac experienced anorexia. This incidence is approximately sixfold that seen in placebo controls. A weight loss of greater than 5% of body weight occurred in 13% of patients treated with Prozac compared to 4% of placebo and 3% of tricyclic-antidepressant-treated patients. However, only rarely have patients been discontinued from treatment with Prozac because of weight loss.

**Activation of Mania/Hypomania**—During premarketing testing, hypomania or mania occurred in approximately 1% of fluoxetine-treated patients. Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed antidepressants.

**Seizures**—Twelve patients among more than 6,000 evaluated worldwide in the course of premarketing development of fluoxetine experienced convulsions (or events described as possibly having been seizures), a rate of 0.2% that appears to be similar to that associated with other marketed antidepressants. Prozac should be introduced with care in patients with a history of seizures.

**Suicide**—The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for Prozac should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

**The Long Elimination Half-Lives of Fluoxetine and Its Metabolites**—Because of the long elimination half-lives of the parent drug (two to three days) and its major active metabolite (seven to nine days), changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment (see Clinical Pharmacology and Dosage and Administration).

**Use in Patients With Concomitant Illness**—Clinical experience with Prozac in patients with concomitant systemic illness is limited. Caution is advisable in using Prozac in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Fluoxetine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from clinical studies during the product's premarketing testing. However, the electrocardiograms of 312 patients who received Prozac in double-blind trials were retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed. The mean heart rate was reduced by approximately three beats/min.

In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A lower or less frequent dose should be used in patients with cirrhosis.

Since fluoxetine is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. However, until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with fluoxetine, it should be used with caution in such patients.

In patients with diabetes, Prozac may alter glycemic control. Hypoglycemia has occurred during therapy with Prozac, and hyperglycemia has developed following discontinuation of the drug. As is true with many other types of medication when taken concurrently by patients with diabetes, insulin and/or oral hypoglycemic dosage may need to be adjusted when therapy with Prozac is instituted or discontinued.

**Interference With Cognitive and Motor Performance**—Any psychoactive drug may impair judgment, thinking, or motor skills, and patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely.

**Information for Patients**—Physicians are advised to discuss the following issues with patients for whom they prescribe Prozac:

Because Prozac may impair judgment, thinking, or motor skills, patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected.

Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs or alcohol.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast feeding an infant.

Patients should be advised to notify their physician if they develop a rash or hives.

**Laboratory Tests**—There are no specific laboratory tests recommended.

**Drug Interactions**—As with all drugs, the potential for interaction by a variety of mechanisms (ie, pharmacodynamic, pharmacokinetic drug inhibition or enhancement, etc) is a possibility (see Accumulation and Slow Elimination under Clinical Pharmacology).

**Tryptophan**—Five patients receiving Prozac in combination with tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress.

**Monoamine Oxidase Inhibitors**—See Warnings.

**Other Antidepressants**—There have been greater than twofold increases of previously stable plasma levels of other antidepressants when Prozac has been administered in combination with these agents (see Accumulation and

Prozac® (fluoxetine hydrochloride, Dista)

Lithium—There have been reports of both increased and decreased lithium levels when lithium was used concomitantly with fluoxetine. Cases of lithium toxicity have been reported. Lithium levels should be monitored when these drugs are administered concomitantly.

**Diazepam Clearance**—The half-life of concurrently administered diazepam may be prolonged in some patients (see Accumulation and Slow Elimination under Clinical Pharmacology).

**Potential Effects of Coadministration of Drugs Highly Bound to Plasma Proteins**—Because fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another drug that is tightly bound to protein (eg, Coumadin, digoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein-bound fluoxetine by other highly bound drugs (see Accumulation and Slow Elimination under Clinical Pharmacology).

**CNS-Active Drugs**—The risk of using Prozac in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised (see Accumulation and Slow Elimination under Clinical Pharmacology).

**Electroconvulsive Therapy**—There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. A single report of a prolonged seizure in a patient on fluoxetine has been reported.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**—There is no evidence of carcinogenicity, mutagenicity, or impairment of fertility with Prozac.

The dietary administration of fluoxetine to rats and mice for two years at levels equivalent to approximately 7.5 and 9.0 times the maximum human dose (80 mg) respectively produced no evidence of carcinogenicity.

Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutagenicity assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Two fertility studies conducted in rats at doses of approximately five and nine times the maximum human dose (80 mg) indicated that fluoxetine had no adverse effects on fertility. A slight decrease in neonatal survival was noted, but this was probably associated with depressed maternal food consumption and suppressed weight gain.

**Pregnancy—Teratogenic Effects—Pregnancy Category B**—Reproduction studies have been performed in rats and rabbits at doses nine and 11 times the maximum daily human dose (80 mg) respectively and have revealed no evidence of harm to the fetus due to Prozac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

**Labor and Delivery**—The effect of Prozac on labor and delivery in humans is unknown.

**Nursing Mothers**—Because many drugs are excreted in human milk, caution should be exercised when Prozac is administered to a nursing woman. In one breast milk sample, the concentration of fluoxetine plus norfluoxetine was 70.4 ng/mL. The concentration in the mother's plasma was 295.0 ng/mL. No adverse effects on the infant were reported.

**Usage in Children**—Safety and effectiveness in children have not been established.

**Usage in the Elderly**—Prozac has not been systematically evaluated in older patients; however, several hundred elderly patients have participated in clinical studies with Prozac, and no unusual adverse age-related phenomena have been identified. However, these data are insufficient to rule out possible age-related differences during chronic use, particularly in elderly patients who have concomitant systemic illnesses or who are receiving concomitant drugs.

**Hyponatremia**—Several cases of hyponatremia (some with serum sodium lower than 110 mmol/L) have been reported. The hyponatremia appeared to be reversible when Prozac was discontinued. Although these cases were complex with varying possible etiologies, some were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these occurrences have been in older patients and in patients taking diuretics or who were otherwise volume depleted.

**Adverse Reactions: Commonly Observed**—The most commonly observed adverse events associated with the use of Prozac and not seen at an equivalent incidence among placebo-treated patients were: nervous system complaints, including anxiety, nervousness, and insomnia; drowsiness and fatigue or asthenia; tremor; sweating; gastrointestinal complaints, including anorexia, nausea, and diarrhea; and dizziness or lightheadedness.

**Associated With Discontinuation of Treatment**—Fifteen percent of approximately 4,000 patients who received Prozac in US premarketing clinical trials discontinued treatment due to an adverse event. The more common events causing discontinuation included: psychiatric (5.3%), primarily nervousness, anxiety, and insomnia; digestive (3.0%), primarily nausea; nervous system (1.6%), primarily dizziness; body as a whole (1.5%), primarily asthenia and headache; and skin (1.4%), primarily rash and pruritus.

**Incidence in Controlled Clinical Trials**—The table that follows enumerates adverse events that occurred at a frequency of 1% or more among Prozac-treated patients who participated in controlled trials comparing Prozac with placebo. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nongrug factors to the side-effect incidence rate in the population studied.

TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS					
Body System/ Adverse Event*	Percentage of Patients Reporting Event		Body System/ Adverse Event*	Percentage of Patients Reporting Event	
	Prozac (N = 1,730)	Placebo (N = 799)		Prozac (N = 1,730)	Placebo (N = 799)
<b>Nervous</b>			<b>Body as a Whole</b>		
Headache	20.3	15.5	Asthenia	4.4	1.9
Nervousness	14.9	6.5	Infection, viral	3.4	3.1
Insomnia	13.9	7.1	Pain, limb	1.6	1.1
Drowsiness	11.6	6.3	Fever	1.4	—
Anxiety	9.4	5.5	Pain, chest	1.2	1.1
Tremor	7.9	2.4	Allergy	1.2	1.1
Dizziness	5.7	3.3	Influenza	1.2	1.5
Fatigue	4.4	1.1	<b>Respiratory</b>		
Sweated	1.9	1.3	Upper		
<b>Body System/ Adverse Event*</b>			Respiratory		
disturbance	1.7	2.0	infection	7.6	6.0
Libido,	1.6	—	Flu-like	2.8	1.9
decreased	1.6	—	syndrome	2.6	1.3
Light-	1.6	—	Pharyngitis	2.6	2.3
headedness	1.6	—	Nasal	2.6	2.3
Concentration,	1.5	—	congestion	2.6	2.3
decreased	1.5	—	<b>Headache,</b>		
<b>Digestive</b>			sinus	2.3	1.8
Nausea	21.1	10.1	Sinusitis	2.1	2.0
Diarrhea	12.3	7.0	Cough	1.6	1.6
Mouth			Dyspnea	1.4	—
dryness	9.5	6.0	<b>Cardiovascular</b>		
Anorexia	8.7	1.5	Pain, back	1.8	1.0
Dyspepsia	6.4	4.3	Pain, joint	1.2	1.1
Constipation	4.5	3.3	Pain, muscle	1.2	1.0
abdominal	4.4	2.9	<b>Urogenital</b>		
Vomiting	2.4	1.3	Menstruation,		
Taste change	1.8	—	painful	1.9	1.4
Flatulence	1.6	1.1	Sexual		
Gastroenteritis	1.0	1.4	dysfunction	1.9	—
<b>Skin and</b>			Frequent		
<b>Appendages</b>			micturition	1.6	—
Sweating,	8.4	3.9	Urinary tract		
excessive	2.7	1.8	infection	1.2	—
Rash	2.4	1.4	<b>Special Senses</b>		
Pruritus	2.4	1.4	Vision		
			disturbance	2.8	1.8

\*Events reported by at least 1% of Prozac-treated patients are included.  
—Incidence less than 1%.

During clinical testing in the US, multiple doses of Prozac were administered to approximately 5,600 subjects. Unwanted events associated with this exposure were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of unwanted events into a limited (ie, reduced) number of standardized event categories.

In the tabulations which follow, a standard COSTART Dictionary terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the 5,600 individuals exposed to Prozac who experienced an event of the type cited on at least one occasion while receiving Prozac. All reported events are included except those already listed in tables, those COSTART terms so general as to be uninformative, and those events where a drug cause was remote. It is important to emphasize that, although the events reported did occur during treatment with Prozac, they were not necessarily caused by it.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

**Body as a Whole**—Frequent: chills; Infrequent: chills and fever, cyst, face edema, hanger effect, jaw pain, malaise, neck pain, neck rigidity, and pelvic pain; Rare: abdomen enlarged, cellulitis, hydrocephalus, hypothermia, LE syndrome, moniliasis, and serum sickness.

**Cardiovascular System**—Infrequent: angina pectoris, arrhythmia, hemorrhage, hypertension, hypotension, migraine, postural hypotension, syncope, and tachycardia; Rare: AV block first-degree, bradycardia, bundle-branch block, cerebral ischemia, myocardial infarct, thrombophlebitis, vascular headache, and ventricular arrhythmia.

**Digestive System**—Frequent: increased appetite; Infrequent: aphthous stomatitis, dysphagia, eructation, esophagitis, gastritis, gingivitis, glossitis, liver function tests abnormal, melena, stomatitis, thirst; Rare: bloody diarrhea, cholecystitis, cholelithiasis, colitis, duodenal ulcer, enteritis, fecal incontinence, hematemesis, hepatitis, hepatomegaly, hyperchlorhydria, increased salivation, jaundice, liver tenderness, mouth ulceration, salivary gland enlargement, stomach ulcer, tongue discoloration, and tongue edema.

**Endocrine System**—Infrequent: hypothyroidism; Rare: goiter and hyperthyroidism.

**Hematologic and Lymphatic System**—Infrequent: anemia and lymphadenopathy; Rare: bleeding time increased, blood dyscrasia, leukopenia, lymphocytosis, petechia, purpura, sedimentation rate increased, and thrombocytopenia.

**Metabolic and Nutritional**—Frequent: weight loss; Infrequent: generalized edema, hypoglycemia, peripheral edema, and weight gain; Rare: dehydration, gout, hypercholesterolemia, hyperglycemia, hyperlipemia, hypoglycemic reaction, hypokalemia, hyponatremia, and iron deficiency anemia.

**Musculoskeletal System**—Infrequent: arthritis, bone pain, bursitis, tenosynovitis, and twitching; Rare: bone necrosis, chondrodystrophy, muscle hemorrhage, myositis, osteoporosis, pathological fracture, and rheumatoid arthritis.

**Nervous System**—Frequent: abnormal dreams and agitation; Infrequent: abnormal gait, acute brain syndrome, akathisia, amnesia, apathy, ataxia, buccoglossal syndrome, CNS stimulation, convulsion, delusions, depersonalization, emotional lability, euphoria, hallucinations, hostility, hyperkinesia, hypesthesia, incoordination, libido increased, manic reaction, neuralgia, neuropathy, paranoid reaction, psychosis, and vertigo; Rare: abnormal electroencephalogram, antisocial reaction, chronic brain syndrome, circumoral paresthesia, CNS depression, coma, dysarthria, dystonia, extrapyramidal syndrome, hyperreflexia, hysteria, myoclonus, nystagmus, paralysis, reflexes decreased, stupor, and torticollis.

**Respiratory System**—Frequent: bronchitis, rhinitis, and yawn; Infrequent: asthma, epistaxis, hiccup, hyperventilation, and pneumonia; Rare: apnea, hemoptysis, hypoxia, larynx edema, lung edema, lung fibrosis/alveolitis, and pleural effusion.

**Skin and Appendages**—Infrequent: acne, alopecia, contact dermatitis, dry skin, herpes simplex, maculopapular rash, and urticaria; Rare: eczema, erythema multiforme, fungal dermatitis, herpes zoster, hirsutism, psoriasis, purpuric rash, pustular rash, seborrhea, skin discoloration, skin hypertrophy, subcutaneous nodule, and vesiculobullous rash.

**Special Senses**—Infrequent: amblyopia, conjunctivitis, ear pain, eye pain, mydriasis, photophobia, and tinnitus; Rare: blepharitis, cataract, corneal lesion, deafness, diplopia, eye hemorrhage, glaucoma, iritis, ptosis, strabismus, and taste loss.

**Urogenital System**—Infrequent: abnormal ejaculation, amenorrhea, breast pain, cystitis, dysuria, fibrocystic breast, impotence, leukorrhea, menopause, menorrhagia, ovarian disorder, urinary incontinence, urinary retention, urinary urgency, urination impaired, and vaginitis; Rare: abortion, albuminuria, breast enlargement, dyspareunia, epididymitis, female lactation, hematuria, hypomenorrhea, kidney calculus, metrorrhagia, orchitis, polyuria, pyelonephritis, pyuria, salpingitis, urethral pain, urethritis, urinary tract disorder, urolithiasis, uterine hemorrhage, uterine spasm, and vaginal hemorrhage.

**Postmarketing Reports**—Voluntary reports of adverse events temporally associated with Prozac that have been received since market introduction and which may have no causal relationship with the drug include the following: vaginal bleeding after drug withdrawal, hyperprolactinemia, thrombocytopenia, and confusion.

**Overdose: Human Experience**—As of December 1987, there were two deaths among approximately 38 reports of acute overdose with fluoxetine, either alone or in combination with other drugs and/or alcohol. One death involved a combined overdose with approximately 1,800 mg of fluoxetine and an undetermined amount of meprobamate. Plasma concentrations of fluoxetine and meprobamate were 4.57 mg/L and 4.18 mg/L respectively. A second death involved three drugs yielding plasma concentrations as follows: fluoxetine, 1.93 mg/L; norfluoxetine, 1.10 mg/L; codeine, 1.80 mg/L; temazepam, 3.80 mg/L.

One other patient who reportedly took 3,000 mg of fluoxetine experienced two grand mal seizures that remitted spontaneously without specific anticonvulsant treatment (see Management). The actual amount of drug absorbed may have been less due to vomiting.

Nausea and vomiting were prominent in overdoses involving higher fluoxetine doses. Other prominent symptoms of overdose included agitation, restlessness, hypomania, and other signs of CNS excitation. Except for the two deaths noted above, all other overdose cases recovered without residual.

Since introduction, a single death attributed to overdose of fluoxetine alone has been reported.

PV 2474 DPP

[090789]

Additional information available to the profession on request.



**Dista Products Company**  
Division of Eli Lilly and Company  
Indianapolis, Indiana 46285

FL-4912-T-949336

Prozac® (fluoxetine hydrochloride, Dista)

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MARCH 1990

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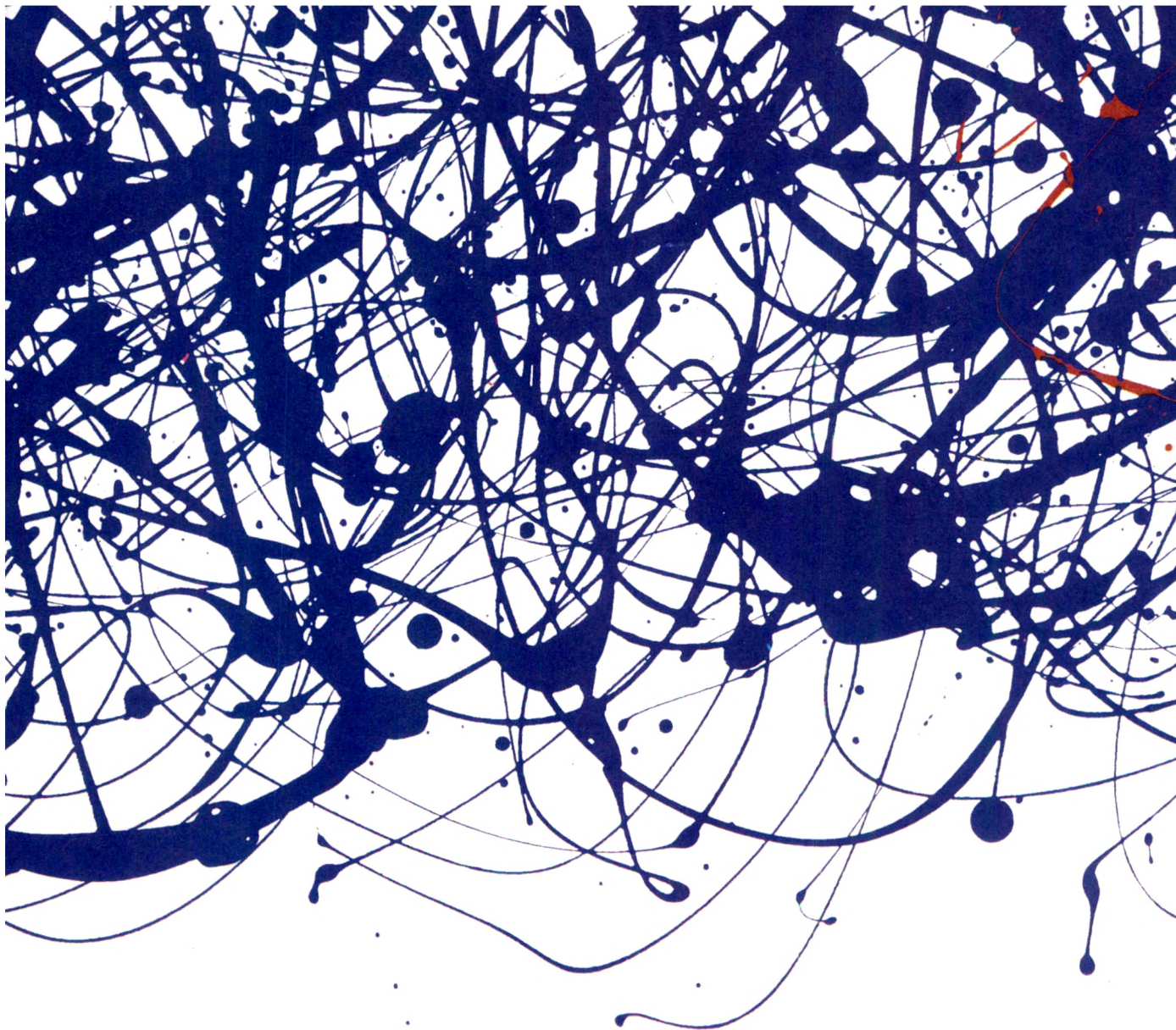
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# With depression..

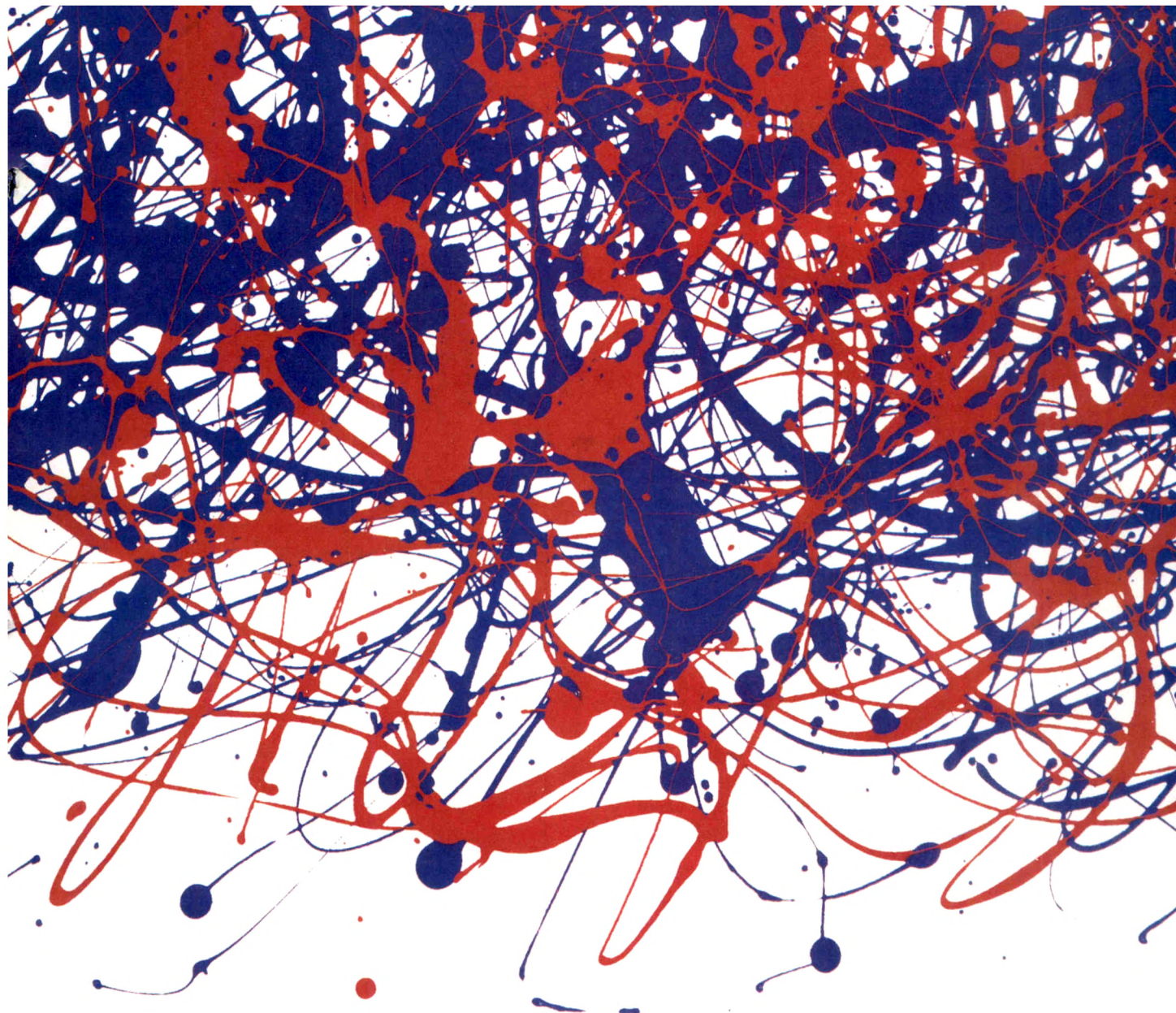
In a clinical trial, XANAX was effective in reducing anxiety symptoms associated with moderate to severe depression.\*

Patients taking XANAX should be alerted to possible additive CNS depressant effects when it is administered with other medications that produce CNS depression.

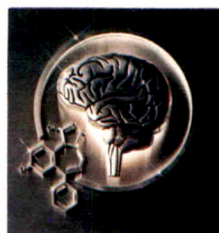
The usual starting dosage of XANAX is 0.25 to 0.5 mg t.i.d.

\*Data on file. The Upjohn Company





you often find anxiety



TABLETS 0.5 MG  
**Xanax**<sup>®</sup>  
alprazolam<sup>®</sup>

**For anxiety associated with  
depression**

**Upjohn**

Please see adjacent page for brief summary of prescribing information.

The Upjohn Company  
Kalamazoo, Michigan 49001, USA

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**XANAX® Tablets**  
(alprazolam, C)

**INDICATIONS AND USAGE**

Anxiety disorders, short-term relief of the symptoms of anxiety and anxiety associated with depression. Anxiety or tension associated with the stress of everyday life usually does not require an anxiolytic. Effectiveness for more than four months has not been established; periodically reassess the usefulness of the drug for the individual patient.

**CONTRAINDICATIONS**

Sensitivity to XANAX or other benzodiazepines, and in acute narrow angle glaucoma.

**WARNINGS**

XANAX is not of value in treating psychosis and should not be used in lieu of appropriate treatment. Patients receiving XANAX should be cautioned about hazardous occupations or activities requiring full alertness and also about simultaneous ingestion of alcohol or other CNS depressants.

Benzodiazepines can cause fetal harm in pregnant women; hence women who may become pregnant should be warned. Avoid during the first trimester. Withdrawal seizures have been reported upon rapid dose reduction or abrupt discontinuation; thus reduce dose gradually (See Drug Abuse and Dependence and Dosage and Administration.)

**PRECAUTIONS**

**General:** If XANAX is combined with other psychotropics or anticonvulsants consider drug potentiation. (See Drug Interactions.) Use the usual precautions in patients with renal or hepatic impairment and regarding prescription size in depressed and suicidal patients. In elderly and debilitated patients, use the lowest possible dose. (See Dosage and Administration.) Hypomania and mania has been reported in depressed patients.

**Information for Patients:** Alert patients about: (a) consumption of alcohol and drugs; (b) possible fetal abnormalities; (c) operating machinery or driving; (d) not increasing dose of the drug due to risk of dependence; (e) not stopping the drug abruptly. **Laboratory Tests:** Not ordinarily required in otherwise healthy patients. **Drug Interactions:** Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Plasma levels of imipramine and desipramine are increased. Pharmacokinetic interactions with other drugs have been reported. Cimetidine can delay clearance of benzodiazepines. **Drug/Laboratory Test Interactions:** No consistent pattern for a drug or test. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** No carcinogenic potential or impairment of fertility in rats. **Pregnancy:** See Warnings. **Nonteratogenic Effects:** The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms, neonatal flaccidity and respiratory problems. **Labor and Delivery:** No established use. **Nursing Mothers:** Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. **Pediatric Use:** Safety and effectiveness in children below the age of 18 have not been established.

**ADVERSE REACTIONS**

Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

**Central nervous system:** Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. **Gastrointestinal:** Dry mouth, constipation, diarrhea, nausea, vomiting, and increased salivation. **Cardiovascular:** Tachycardia/palpitations, and hypotension. **Sensory:** Blurred vision. **Musculoskeletal:** Rigidity and tremor. **Cutaneous:** Dermatitis/allergy. **Other side effects:** Nasal congestion, weight gain, and weight loss.

Withdrawal seizures with rapid decrease or abrupt discontinuation. (See Warnings.)

The following adverse events have been reported with benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, seizures, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence, and urinary retention.

Paradoxical reactions such as stimulation, agitation, rage, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur discontinue the drug.

During prolonged treatment periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes of unknown significance have been observed.

Liver enzyme elevations, gynecomastia and galactorrhea have been reported but no causal relationship was established.

**DRUG ABUSE AND DEPENDENCE**

**Physical and Psychological Dependence:** Withdrawal symptoms including seizures have occurred following abrupt discontinuance or rapid dose reduction of benzodiazepines. (See Warnings.) Dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. **Controlled Substance Class:** XANAX is a controlled substance and has been assigned to schedule IV.

**OVERDOSAGE**

Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

**DOSAGE AND ADMINISTRATION**

Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy by no more than 0.5 mg every three days.

**HOW SUPPLIED**

XANAX Tablets are available as 0.25 mg, 0.5 mg, and 1 mg tablets.

**CAUTION:** FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

B-8-S

J-2252

November, 1989

**Upjohn**

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Kalamazoo, Michigan 49001, USA

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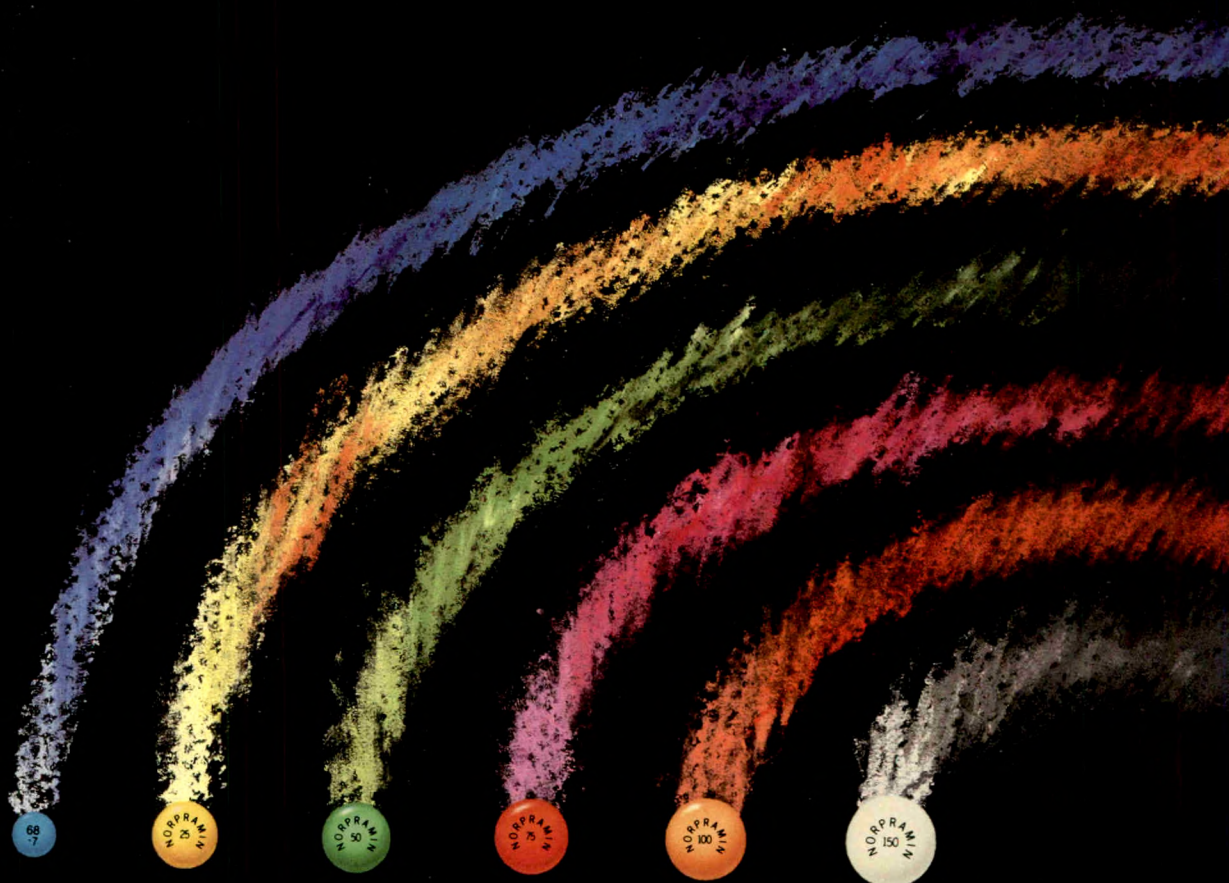
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**A spectrum of reasons  
to write D.A.W.  
when you prescribe**



**Norpramin<sup>®</sup>** 10, 25, 50, 75, 100, 150 mg  
(desipramine hydrochloride tablets USP)  
A logical choice among antidepressants

**A 25-year history** of proven clinical usefulness with unsurpassed **flexibility of dosage** provided by 6 tablet strengths, **color coded** to ensure exact identification. It also offers **dose equivalence** that permits prescribing one tablet of greater strength in place of multiple doses of lesser strengths, resulting in **increased patient compliance** and greater than **20% cost savings**.

(Brief Summary of Prescribing Information appears on the next page.)





**Ensure the maximum benefits of Norpramin by specifying "Dispense As Written."**

- A 25-year record of efficacy in relieving the symptoms of depression\*
- Less anticholinergic activity than amitriptyline or doxepin\*
- Usually no excessive daytime drowsiness (see Warnings)†

## Norpramin (desipramine hydrochloride tablets USP)

\*References supporting these statements available from MERRELL DOW PHARMACEUTICALS INC., Cincinnati, Ohio 45242.

†Norpramin does not usually inhibit normal activity, although patients should be cautioned against driving or operating machinery if drowsiness occurs (see Warnings, Precautions, and Adverse Reactions).

# Norpramin® 10, 25, 50, 75, 100, 150 mg (desipramine hydrochloride tablets USP)

## Norpramin® (desipramine hydrochloride tablets USP)

### BRIEF SUMMARY

**CAUTION:** Federal law prohibits dispensing without prescription.

### INACTIVE INGREDIENTS

The following inactive ingredients are contained in all dosage strengths: acacia, calcium carbonate, corn starch, D&C Red No. 30 and D&C Yellow No. 10 (except 10 mg and 150 mg), FD&C Blue No. 1, FD&C Red No. 3, FD&C Yellow No. 6, hydrogenated soy oil, iron oxide, light mineral oil, magnesium stearate, mannitol, polyethylene glycol 8000, pregelatinized corn starch, sodium benzoate (except 150 mg), sucrose, talc, titanium dioxide, and other ingredients.

### CLINICAL PHARMACOLOGY

#### Metabolism

The rate of metabolism of tricyclic antidepressants varies widely from individual to individual, chiefly on a genetically determined basis. In general, the elderly metabolize tricyclic antidepressants more slowly than do younger adults.

Certain drugs, particularly the psychostimulants and the phenothiazines, increase plasma levels of concomitantly administered tricyclic antidepressants through competition for the same metabolic enzyme systems. Other substances, particularly barbiturates and alcohol, induce liver enzyme activity and thereby reduce tricyclic antidepressant plasma levels. Similar effects have been reported with tobacco smoke.

Additional information on metabolism appears in Full Prescribing Information.

### CONTRAINDICATIONS

Desipramine hydrochloride should not be given in conjunction with, or within 2 weeks of, treatment with an MAO inhibitor drug; hyperpyretic crises, severe convulsions, and death have occurred in patients taking MAO inhibitors and tricyclic antidepressants. When Norpramin (desipramine hydrochloride) is substituted for an MAO inhibitor, at least 2 weeks should elapse between treatments. Norpramin should then be started cautiously and should be increased gradually.

The drug is contraindicated in the acute recovery period following myocardial infarction. It should not be used in those who have shown prior hypersensitivity to the drug. Cross sensitivity between this and other dibenzazepines is a possibility.

### WARNINGS

- Extreme caution should be used when this drug is given in the following situations:
  - In patients with cardiovascular disease, because of the possibility of conduction defects, arrhythmias, tachycardias, strokes, and acute myocardial infarction.
  - In patients with a history of urinary retention or glaucoma, because of the anticholinergic properties of the drug.
  - In patients with thyroid disease or those taking thyroid medication, because of the possibility of cardiovascular toxicity, including arrhythmias.
  - In patients with a history of seizure disorder, because this drug has been shown to lower the seizure threshold.
- This drug is capable of blocking the antihypertensive effect of guanethidine and similarly acting compounds.
- USE IN PREGNANCY**  
Safe use of desipramine hydrochloride during pregnancy and lactation has not been established; therefore, if it is to be given to pregnant patients, nursing mothers, or women of childbearing potential, the possible benefits must be weighed against the possible hazards to mother and child. Animal reproductive studies have been inconclusive.
- USE IN CHILDREN**  
Norpramin (desipramine hydrochloride) is not recommended for use in children since safety and effectiveness in the pediatric age group have not been established. (See ADVERSE REACTIONS, Cardiovascular.)
- The patient should be cautioned that this drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.
- In patients who may use alcohol excessively, it should be borne in mind that the potentiation may increase the danger inherent in any suicide attempt or overdose.

### PRECAUTIONS

- It is important that this drug be dispensed in the least possible quantities to depressed outpatients, since suicide has been accomplished with this class of drug. Ordinary prudence requires that children not have access to this drug or to potent drugs of any kind, if possible, this drug should be dispensed in containers with child-resistant safety closures. Storage of this drug in the home must be supervised responsibly.
- If serious adverse effects occur, dosage should be reduced or treatment should be altered.
- Norpramin (desipramine hydrochloride) therapy in patients with manic-depressive illness may induce a hypomanic state after the depressive phase terminates.
- The drug may cause exacerbation of psychosis in schizophrenic patients.
- Close supervision and careful adjustment of dosage are required when this drug is given concomitantly with anticholinergic or sympathomimetic drugs.
- Patients should be warned that while taking this drug their response to alcoholic beverages may be exaggerated.
- Clinical experience in the concurrent administration of ECT and antidepressant drugs is limited. Thus, if such treatment is essential, the possibility of increased risk relative to benefits should be considered.
- If Norpramin (desipramine hydrochloride) is to be combined with other psychotropic agents such as tranquilizers or sedative/hypnotics, careful consideration should be given to the pharmacology of the agents employed since the sedative effects of Norpramin and benzodiazepines (e.g., chlordiazepoxide or diazepam) are additive. Both the sedative and anticholinergic effects of the major tranquilizers are also additive to those of Norpramin.
- Concurrent administration of cimetidine and tricyclic antidepressants can produce clinically significant increases in the plasma levels of the tricyclic antidepressants. Conversely, decreases in plasma levels of the tricyclic antidepressants have been reported upon discontinuation of cimetidine which may result in the loss of the therapeutic efficacy of the tricyclic antidepressant.
- This drug should be discontinued as soon as possible prior to elective surgery because of the possible cardiovascular effects. Hypertensive episodes have been observed during surgery in patients taking desipramine hydrochloride.
- Both elevation and lowering of blood sugar levels have been reported.
- Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is evidence of pathologic neutrophil depression.

### ADVERSE REACTIONS

Note: Included in the following listing are a few adverse reactions that have not been reported with this specific drug. However, the pharmacologic similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when Norpramin (desipramine hydrochloride) is given.

**Cardiovascular:** hypotension, hypertension, tachycardia, palpitation, arrhythmias, heart block, myocardial infarction, stroke. There has been a report of an "acute collapse" and

"sudden death" in an eight-year old (18 kg) male, treated for two years for hyperactivity. (See WARNINGS, Use in Children.)

**Psychiatric:** confusional states (especially in the elderly) with hallucinations, disorientation, delusions, anxiety, restlessness, agitation, insomnia and nightmares; hypomania; exacerbation of psychosis.

**Neurologic:** numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures; alteration in EEG patterns; tinnitus.

**Anticholinergic:** dry mouth, and rarely associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis, increased intraocular pressure, constipation, paralytic ileus; urinary retention, delayed micturition, dilatation of urinary tract.

**Allergic:** skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight), edema (of face and tongue or general), drug fever, cross sensitivity with other tricyclic drugs.

**Hematologic:** bone marrow depressions including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

**Gastrointestinal:** anorexia, nausea and vomiting, epigastric distress, peculiar taste, abdominal cramps, diarrhea, stomatitis, black tongue.

**Endocrine:** gynecostasia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence, painful ejaculation, testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate antidiuretic hormone secretion (SIADH).

**Other:** jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration, flushing, urinary frequency, nocturia; parotid swelling; drowsiness, dizziness, weakness and fatigue, headache, alopecia.

**Withdrawal Symptoms:** Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

### OVERDOSAGE

There is no specific antidote for desipramine, nor are there specific phenomena of diagnostic value characterizing poisoning by the drug.

Within an hour of ingestion the patient may become agitated or stuporous and then comatose. Hypotension, shock, and renal shutdown may ensue. Grand mal seizures, both early and late after ingestion, have been reported. Hyperactive reflexes, hyperpyrexia, muscle rigidity, vomiting, and EEG evidence of impaired conduction may occur. Serious disturbances of cardiac rate, rhythm, and output can occur. The precepts of early evaluation of the ingested material and subsequent support of respiration (airway and movement), circulation, and renal output apply.

The principles of management of coma and shock by means of the mechanical respirator, cardiac pacemaker, monitoring of central venous pressure, and regulation of fluid and acid-base balance are well known in most medical centers and are not further discussed here.

Because CNS involvement, respiratory depression, and cardiac arrhythmia can occur suddenly, hospitalization and close observation are generally advisable, even when the amount ingested is thought to be small or the initial degree of intoxication appears slight or moderate. Most patients with EEG abnormalities should have continuous cardiac monitoring for at least 72 hours and be closely observed until well after cardiac status has returned to normal; relapses may occur after apparent recovery.

The slow intravenous administration of physostigmine salicylate has been reported to reverse most of the anticholinergic cardiovascular and CNS effects of overdose with tricyclic antidepressants. In adults, 1 to 3 mg has been reported to be effective. In children, the dose should be started with 0.5 mg and repeated at 5-minute intervals to determine the minimum effective dose; no more than 2 mg should be given. Because of the short duration of action of physostigmine, the effective dose should be repeated at 30-minute to 60-minute intervals, as necessary. Rapid injection should be avoided to reduce the possibility of physostigmine-induced convulsions.

Other possible therapeutic considerations include:

- Dialysis: Desipramine is found in low concentration in the serum, even after a massive oral dose. In vitro experiments in which blood bank blood was used indicate that it is very poorly dialyzed. Because of indications that the drug is secreted in gastric juice, constant gastric lavage has been suggested.
- Pharmacologic treatment of shock: Since desipramine potentiates the action of such vasopressor agents as levaterenol and metaraminol, they should be used only with caution.
- Pharmacologic control of seizures: Intravenous barbiturates are the treatment of choice for the control of grand mal seizures. One may, alternatively, consider the parenteral use of diphenylhydantoin, which has less central depressant effect but also has an effect on heart rhythm that has not yet been fully defined.
- Pharmacologic control of cardiac function: Severe disturbances of cardiac rate, rhythm, and output are probably the initiating events in shock. Intravascular volume must be maintained by i.v. fluids. Digitalization should be carried out early in view of the fact that a positive inotropic effect can be achieved without increase in cardiac work. Many of the cardiodynamic effects of digitalis are the exact opposite of those of massive doses of desipramine (animal studies).

Product Information as of January, 1989

Y398D

MERRELL DOW PHARMACEUTICALS INC.  
Cincinnati, Ohio 45215, U.S.A.

**Merrell Dow**

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# Introducing **HALDOL<sup>®</sup> Decanoate 100** (HALOPERIDOL) INJECTION

**Less volume per injection  
can enhance patient acceptance**

New 100 mg/mL formulation is twice the concentration  
of the original 50 mg/mL decanoate formulation

- For many patients, fewer injections per dose may reduce anxiety and enhance patient compliance
- Multi-dose vial packaging means convenience for you and your staff



Please see brief summary of Prescribing Information on next page.

During dose adjustment or episodes of exacerbation of psychotic symptoms, therapy with HALDOL Decanoate 100 or HALDOL Decanoate 50 can be supplemented with short-acting forms of HALDOL<sup>®</sup> (haloperidol). The side effects of the decanoate products are those of HALDOL. The prolonged action of HALDOL Decanoate 100 and HALDOL Decanoate 50 should be considered in the management of side effects.

**McNEIL  
PHARMACEUTICAL**  
McNEILAB, INC., Spring House, PA 19477

**HALDOL<sup>®</sup> Decanoate 100**  
(HALOPERIDOL) INJECTION 100mg/mL

**HALDOL<sup>®</sup> Decanoate 50**  
(HALOPERIDOL) INJECTION 50mg/mL



# HALDOL® Decanoate 100

(HALOPERIDOL) INJECTION 100mg/mL

# HALDOL® Decanoate 50

(HALOPERIDOL) INJECTION 50mg/mL

For IM Injection Only

The following is a brief summary only. Before prescribing, see complete prescribing information in HALDOL and HALDOL Decanoate product labeling.

**Contraindications:** Since the pharmacologic and clinical actions of HALDOL Decanoate 50 and HALDOL Decanoate 100 are attributed to HALDOL haloperidol as the active medication, Contraindications, Warnings, and additional information are those of HALDOL, modified to reflect the prolonged action.

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

**Warnings:** *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

*Neuroleptic Malignant Syndrome (NMS):* A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with HALDOL.

*Usage in Pregnancy:* (see PRECAUTIONS—Usage in Pregnancy) *Combined Use With Lithium:* (see PRECAUTIONS—Drug Interactions)

*General:* Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS—Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

**Precautions:** Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinson medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intracocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL.

The 1, 5, 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

*Information for Patients:* Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

*Drug Interactions:* Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear. As with other antipsychotic agents, it should be noted that HALDOL may be capable of potentiating CNS depressants such as anesthetics, opiates, and alcohol.

*Carcinogenesis, Mutagenesis and Impairment of Fertility:* No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsomal activation assay.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

*Usage in Pregnancy:* Pregnancy Category C. Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards to the fetus.

*Nursing Mothers:* Infants should not be nursed during drug treatment.

*Pediatric Use:* Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

**Adverse Reactions:** Adverse reactions following the administration of HALDOL Decanoate 50 or HALDOL Decanoate 100 are those of HALDOL haloperidol. Since vast experience has accumulated with HALDOL, the adverse reactions are reported for that compound as well as for haloperidol decanoate. As with all injectable medications, local tissue reactions have been reported with haloperidol decanoate.

*CNS Effects: Extrapyramidal Reactions—*Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which when first observed were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases. *Withdrawal Emergent Neurological Signs—*Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available HALDOL should be gradually withdrawn. *Tardive Dyskinesia—*As with all antipsychotic agents HALDOL has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients irreversible. The syndrome is characterized by rhythmic involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk. There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked. It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop. *Tardive Dystonia—*Tardive dystonia, not associated with the above syndrome, has also been reported. Tardive dystonia is characterized by delayed onset of choreic or dystonic movements, is often persistent, and has the potential of becoming irreversible. *Other CNS Effects—*Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

*Body as a Whole:* Neuroleptic malignant syndrome (NMS), hyperpyrexia and heat stroke have been reported with HALDOL. (See WARNINGS for further information concerning NMS.) *Cardiovascular Effects:* Tachycardia, hypotension, hypertension and ECG changes. *Hematologic Effects:* Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication. *Liver Effects:* Impaired liver function and/or jaundice. *Dermatologic Reactions:* Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. *Endocrine Disorders:* Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia. *Gastrointestinal Effects:* Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. *Autonomic Reactions:* Dry mouth, blurred vision, urinary retention, diaphoresis, and priapism. *Respiratory Effects:* Laryngospasm, bronchospasm and increased depth of respiration. *Special Senses:* Cataracts, retinopathy and visual disturbances. *Other:* Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

**IMPORTANT:** Full directions for use should be read before HALDOL or HALDOL Decanoate products are administered or prescribed.

For information on symptoms and treatment of overdosage, see full prescribing information.

The short-acting HALDOL injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

McNeil Pharmaceutical, McNEILAB, INC., Spring House, PA 19477

8/23/89

## PSYCHIATRIST IN CHIEF

Kingston Psychiatric Hospital in cooperation with Queen's University is seeking applications for the position of Psychiatrist-in-Chief. We seek to attract an experienced psychiatrist interested in an academic career involving teaching and research in psychiatry, coupled with the challenge of medical administration and patient care.

The hospital is located on 127 acres of waterfront property in the southwest end of the city and offers a full range of adult psychiatric services with specialized rehabilitation, forensic and geriatric units. Kingston Psychiatric Hospital is active in teaching Psychiatric Residents as well as Interns, Medical Students and Residents in other training programs and conducts psychiatric research.

The successful applicant, in partnership with senior hospital and university staff, will be responsible for the provision of first class patient services integrated with mental health services in the community, the education of future health professionals, and the conduct of research. He/she will be in charge of all medical affairs and participate in the overall management of the hospital.

Qualifications for the position include eligibility for licensure to practice medicine in Ontario with certification from R.C.P.S. (Canada) as a specialist in psychiatry. He/she must also be qualified for academic appointment to Queen's University's Department of Psychiatry. The incumbent must be an experienced psychiatrist with at least 5 years of clinical practice experience within a hospital setting and proven skills in administration.

Contract, G.F.T. or Civil Service appointment is possible. Please forward Curriculum Vitae and names of three references by May 31, 1990 to:

*Mr. W.A. Barnett, Administrator  
Kingston Psychiatric Hospital  
P.O. Box 603  
Kingston, Ontario K7L 4X3*

## DIRECTOR OF PSYCHIATRY

Saint Michael's Medical Center in Newark, New Jersey, is inviting applications for the position of Director of Psychiatry.

Saint Michael's Medical Center is a 411-bed acute care, regional referral and teaching hospital with centers of excellence in cardiology, cardiac surgery, blood research and infectious diseases.

The Director holds responsibility for all aspects of administration, teaching and research within the department. The position carries an academic appointment at the Seton Hall University School of Graduate Medical Education.

We seek a highly motivated candidate who is a board certified psychiatrist with demonstrated ability in leadership, teaching and program development.

Qualified applicants should forward a curriculum vitae to:

**Ms. Maureen Fisher, Medical Staff Office**



**Saint Michael's Medical Center**

268 Dr. Martin Luther King, Jr. Blvd.  
Newark, New Jersey 07102

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The Department of Veterans Affairs (VA) is America's largest and most comprehensive health care system. A VA Medical Center offers a dynamic health care environment in which physicians, nurses, therapists and technicians work in concert: teaming, sharing and learning from each other. Immediate openings exist nationwide for Psychiatrists, particularly those who are Board Certified by an American Specialty Board.

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- Qualification requirements:
- **Must** hold a degree, a Doctor of Medicine or an equivalent degree from an approved school.
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- **Must** have completed an approved 1-year internship, or the equivalent.
- **Must** be a citizen of the United States. (Non-citizens may be appointed on a temporary basis in rare instances.)

Your salary will be based on the number of years in practice, training received, and professional achievements. Special pay based upon such factors as board certification, geographic location and scarce medical specialty may apply.

Benefits include health and life insurance, attractive retirement plan, 30 days paid vacation, 15 days sick leave, 10 paid holidays and many educational opportunities. In addition, Federal malpractice protection is provided at no cost to you.

To explore a health care career with us, contact the VA Medical Center near you or call toll-free, 1-800-368-6008 (in Virginia, 1-800-552-3045).

You may also write for an application package. Address your inquiry to:

**Department of  
Veterans Affairs  
Physician Placement  
Service  
P.O. Box 24269  
Richmond, Virginia 23224**

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AFFILIATION

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## A defense against cancer can be cooked up in your kitchen.

There is evidence that diet and cancer are related. Some foods may promote cancer, while others may protect you from it.

Foods related to lowering the risk of cancer of the larynx and esophagus all have high amounts of carotene, a form of Vitamin A which is in cantaloupes, peaches, broccoli, spinach, all dark green leafy vegetables, sweet potatoes, carrots, pumpkin, winter squash, and tomatoes, citrus fruits and brussels sprouts.

Foods that may help reduce the risk of gastrointestinal and respiratory tract cancer are cabbage, broccoli, brussels sprouts, kohlrabi, cauliflower.

Fruits, vegetables and whole-grain cereals such as oatmeal, bran and wheat may help lower the risk of colorectal cancer.

Foods high in fats, salt- or nitrite-cured foods such as ham, and fish and types of sausages smoked by traditional methods should be eaten in moderation.

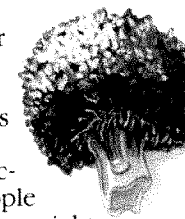
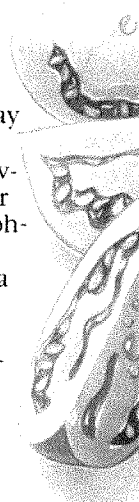
Be moderate in consumption of alcohol also.

A good rule of thumb is cut down on fat and don't be fat. Weight reduction may lower cancer risk. Our 12-year study of nearly a million Americans uncovered high cancer risks particularly among people 40% or more overweight.

Now, more than ever, we know you can cook up your own defense against cancer. So eat healthy and be healthy.

No one faces  
cancer alone.

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# PSYCHIATRISTS

Excellent opportunity for psychiatrists at The Allentown Hospital — Lehigh Valley Hospital Center, an 830-bed tertiary care teaching hospital, with 55 inpatient psychiatric beds (11 adolescent and 44 adult). The hospital is seeking an Inpatient Medical Director, consultation-liaison psychiatrist and a mental health clinic psychiatrist. Positions combine part-time salary with a private practice component. Board certification or board eligibility required. Competitive salary and private practice support. The hospital trains 70 residents in six free-standing residency programs, and is a clinical campus of Hahnemann University in Philadelphia.

Serving a population of close to one million people, the hospital is located in Allentown, PA, a cosmopolitan city which is one and one-half hours west of New York City and one hour north of Philadelphia. Allentown's public school system is highly rated by colleges and there are nine colleges and universities in the area. Interested candidates please send CV, in confidence, to: David A. Tomb, M.D., Chairman, Department of Psychiatry, c/o HealthSearch, 50 College Drive, Allentown, PA 18104, (215) 778-7993.

## PARTNERS PRACTICING GOOD MEDICINE.

The Southern California Permanente Medical Group is a well-established, prepaid health care program. Our multispecialty group practice is a partnership composed of and managed by SCPMG physicians.

We are currently accepting applications from board eligible/certified inpatient or outpatient **Psychiatrists** for the following positions:

General Adult, Child/Adolescent,  
Consultation and Liaison,  
and Alcohol and Drug Dependency.

We would like to invite you to visit with us at the **American Psychiatric Association Annual Meeting in New York, from May 12-17, 1990. See us at Booth #126.** Or, to pre-arrange a personal interview with our psychiatrists during this week, please call us at (800) 328-5278 (CA) or (800) 541-7946 (US).

If you are unable to attend and would like a physician application, send your CV to Irwin P. Goldstein, M.D., Associate Medical Director, SCPMG, Dept. 008, Walnut Center, Pasadena, CA 91188-8013.

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# PSYCHIATRIST

**ANNAPOLIS VALLEY, NOVA SCOTIA, CANADA**

**CONTRACT AVAILABLE \$134,000 PER ANNUM FOR  
CANADIAN CERTIFIED PSYCHIATRIST**

There is a vacancy for a staff psychiatrist in the Mental Health Division of Valley Health Services Association (V.H.S.A.).

The Division offers comprehensive services to a population of approximately 85,000 in Annapolis and Kings Counties, Nova Scotia. Out-patient clinics are held in four locations from historic Annapolis Royal in the west to the university town of Wolfville in the east. The service is based in the regional general hospital at Kentville, in which the partial hospitalization program is located. A thirty-bed inpatient unit in the new regional general hospital at Kentville is expected to open in approximately two years. Currently, two inpatient units, totalling forty-two beds, are located at Waterville. The Regional Hospital is a little over one hour's drive from Halifax, the Provincial capital.

The Royal College of Physicians and Surgeons of Canada recognizes V.H.S.A. as a teaching unit for the Psychiatry Residency Program of Dalhousie University. Appropriately qualified staff are eligible for faculty appointments in the Department of Psychiatry; Resident training in Community Psychiatry has now begun, as has the assignment of Final Year Medical Students for eight-week psychiatry rotations.

Qualifications required are eligibility for licensure to practice in Nova Scotia and Certification in Psychiatry by the Royal College of Physicians and Surgeons of Canada, or equivalent. Candidates not yet certified, but eligible to take C.R.C.P.C. examinations, may be considered. Preference is given to Canadian citizens or landed immigrants.

Requests for application forms should be submitted, along with a detailed curriculum vitae and names of three references to:

*Dr. Aindrias O'Breasail  
Interim Medical Director, Medical Health Division  
Valley Health Services Association  
186 Park Street  
Kentville, Nova Scotia  
B4N 1M7*

# NAVAL HOSPITAL PORTSMOUTH, VA

## PSYCHIATRIST PORTSMOUTH, VA

Naval Hospital, Portsmouth, VA is seeking a dynamic, self-motivated BE/BC, Child Psychiatrist to provide professional support to a new multidisciplinary program. Primary focus is on psychiatric evaluation and treatment of military beneficiaries as well as consultation with the Exceptional Family Member Program team.

This hospital is a teaching facility which includes psychiatric and pediatric residencies.

For additional information, contact Jan Seaver, Civilian Personnel Office at (804) 398-5776.

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## The University of Queensland

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### Professor/Associate Professor of Child Psychiatry Director of Child Psychiatry

Applications are called for appointment to the newly established combined position of Foundation Professor or Associate Professor of Child Psychiatry (The University of Queensland), and Director of Child Psychiatry (Royal Children's Hospital, Brisbane).

Applications should have qualifications registrable in the Medical Specialty of Psychiatry with the Medical Board of Queensland. They should hold the Certificate in Child Psychiatry (RANZCP), or have had the experience equivalent to that required for that Certificate. Applicants should also possess a distinguished research record and extensive clinical experience at consultant level. They should have a demonstrated ability in teaching at both undergraduate and postgraduate levels.

The appointee will be expected to have significant clinical and teaching practice within the Royal Children's Hospital, Brisbane. The appointment will be either the University Department of Child Health or Department of Psychiatry, as determined in discussion with the appointee, and will involve formal academic attachment to both Departments.

**Salary:** \$93,490 (Professor) or \$83,471 (Associate Professor), in each case including clinical loading of \$11,707 and state loading of \$15,946. Further information is available from Professor John Pearn, Head, Department of Child Health (07) 253 5323 or Professor Beverley Raphael, Head, Department of Psychiatry (07) 253 5152. Please forward an original plus three copies of application and resume to the Director, Personnel Services, The University of Queensland, Queensland 4072 Australia.

Ref No: 13490.  
Closing Date: 29 June, 1990.

## TENURE TRACK POSITIONS

Several positions, at both senior and junior faculty levels, are available in the expanding Department of Psychiatry at MetroHealth Medical Center, a major teaching hospital of Case Western Reserve University School of Medicine. Board certification preferred. Commitment to academic psychiatry a prerequisite.

### Contact:

*R. Taylor Segraves, M.D., Ph.D.*  
Associate Director  
Department of Psychiatry  
MetroHealth Medical Center  
3395 Scranton Road  
Cleveland, Ohio 44109.

## CHILD AND ADOLESCENT PSYCHIATRIST

Annapolis Valley, Nova Scotia, Canada

CONTRACT AVAILABLE AT \$134,000 PER ANNUM FOR  
PERSON WITH CANADIAN CERTIFICATION

There is a new position for a child and adolescent psychiatrist for the Mental Health Division of Valley Health Services Association (V.H.S.A.) available immediately.

The Division offers a comprehensive service to a population of approximately 85,000 in Annapolis and Kings Counties, Nova Scotia. The successful applicant would work in a multidisciplinary setting and be involved in consultation and treatment in the outpatient clinics and referral agencies. There is the opportunity to work with another child and adolescent psychiatrist, along with skilled social workers, psychologists and community mental health nurses. The area has established excellent working relationships with other child-caring agencies, and there will be opportunity to work with those agencies in developing an emergency assessment center for adolescents. The Mental Health Division is a part of the Regional Hospital which is a one-hour drive from Halifax, and the Regional Hospital offers most specialty services.

The Royal College of Physicians and Surgeons of Canada recognizes V.H.S.A. as a teaching unit for the Psychiatry Residency Program of Dalhousie University. Appropriately qualified staff are eligible for faculty appointments in the Department; Resident training in Community Psychiatry has now begun, as has the assignment of final year Medical Students for eight-week psychiatry rotations.

Qualifications required are eligibility for license to practice in Nova Scotia and Certification in Psychiatry by the Royal College of Physicians and Surgeons of Canada, or equivalent. Candidates not yet certified, but eligible to take C.R.C.P.C. examinations may be considered. Preference is given to Canadian citizens or landed immigrants.

Requests for application form should be submitted, along with a detailed curriculum vitae and names of three references, to:

*Dr. Aindrias O'Breasail*  
Interim Medical Director, Mental Health Division  
Valley Health Services Association  
186 Park Street  
Kentville, Nova Scotia B4N 1M7

## CHAIRPERSON CHILD AND ADOLESCENT PSYCHIATRY

Applications and nominations are invited for the position of **Chairperson, Department of Psychiatry** at the Children's National Medical Center (CNMC) and the Chief, Division of Child and Adolescent Psychiatry at the Department of Psychiatry at George Washington University Medical Center in Washington, D.C. CNMC is a private, 270-bed pediatric teaching hospital, with 180 full-time faculty and 2600 employees. It serves as the Department of Pediatrics for the George Washington University Medical Center.

We seek a candidate who is academically oriented with a distinguished record in clinical activities, teaching and research. Candidates must be board certified in child and adolescent psychiatry. Strong leadership qualities and demonstrated administrative skills are required. Salary will be commensurate with experience and qualifications.


Applications should be received by July 1, 1990. Applicants should forward their Curriculum Vitae and bibliography to:

**Lawrence D'Angelo, M.D., M.P.H.**  
Professor and Chairman  
Department of Adolescent and  
Young Adult Medicine

**Children's National Medical Center**  
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**Stelazine<sup>®</sup>**  
brand of  
trifluoperazine HCl

**Available in Tablets: 1, 2, 5 and 10 mg  
Multiple-dose Vials: 10 mL (2 mg/mL)  
Concentrate: 10 mg/mL**

**Before prescribing, please see brief summary of  
prescribing information on adjacent page.**

**SK&F LAB CO.**



# Stelazine®

brand of  
trifluoperazine HCl

Before prescribing, see complete prescribing information in SK&F Lab Co. literature or PDR. The following is a brief summary.

**Contraindications:** Comatose or greatly depressed states due to C.N.S. depressants, blood dyscrasias; bone marrow depression; liver damage.

**Warnings:** Tardive dyskinesia (TD) may develop in patients treated with neuroleptic (antipsychotic) drugs. The risk of TD and likelihood of irreversibility are thought to increase as duration of treatment and total cumulative neuroleptic dose increase. Much less commonly, the syndrome can develop after relatively brief treatment at low doses. There is no known treatment for TD, although it may remit if neuroleptics are withdrawn. Neuroleptic treatment may suppress signs and symptoms of the syndrome and thereby mask the underlying disease process. To minimize risk of TD, generally reserve chronic neuroleptic treatment for patients who suffer from chronic illness that responds to neuroleptics and for whom alternative, effective, less harmful treatments are not available or appropriate. In patients requiring chronic treatment, the minimal effective dose and shortest duration of treatment should be sought. Periodically reassess need for continued treatment. If signs and symptoms of TD appear, discontinuation of neuroleptics should be considered. [See PRECAUTIONS.]

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported in association with antipsychotic drugs. Clinical manifestations include: Hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment, if available, of any concomitant serious medical problems.

'Stelazine' Concentrate contains sodium bisulfite, which may cause allergic-type reactions including anaphylactic symptoms or asthmatic episodes in certain susceptible people. The prevalence of sulfite sensitivity in the general population is unknown and probably low and is seen more frequently in asthmatic than in non-asthmatic people.

Generally avoid using in patients hypersensitive (e.g., have had blood dyscrasias, jaundice) to any phenothiazine. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery), especially during the first few days' therapy. Additive depressant effect is possible with other C.N.S. depressants, including alcohol. Do not use in pregnancy except when essential and potential benefits clearly outweigh possible hazards. Prolonged jaundice, extrapyramidal signs, hyperreflexia and hyporeflexia have been reported in newborns whose mothers received phenothiazines. There is evidence that phenothiazines are excreted in the breast milk of nursing mothers.

**Precautions:** Since some patients chronically exposed to neuroleptics will develop tardive dyskinesia, it is advised that, if possible, full information about this risk be given to patients or their guardians when chronic use is contemplated.

Use cautiously in angina. Avoid high doses and parenteral use when cardiovascular system is impaired since hypotension has occurred. Antiemetic effect may mask the signs of overdosage of other drugs or obscure diagnosis and treatment of certain physical disorders. Prolonged use of high doses may result in cumulative effects with severe C.N.S. or vasomotor symptoms. If retinal changes occur, discontinue drug. Agranulocytosis, thrombocytopenia, pancytopenia, anemia, cholestatic jaundice, liver damage have been reported. Use cautiously in patients with glaucoma.

Patients with a history of long-term therapy with 'Stelazine' and/or other neuroleptics should be evaluated periodically for possible dosage adjustment or discontinuance of drug therapy. Neuroleptic drugs cause elevated prolactin levels that persist during chronic use. Since approximately one-third of human breast cancers are prolactin-dependent *in vitro*, this elevation is of potential importance if neuroleptic drug use is contemplated in a patient with a previously detected breast cancer. However, clinical and epidemiologic studies to date have not shown an association between the chronic use of neuroleptic drugs and mammary tumorigenesis. Chromosomal aberrations in spermatocytes and abnormal sperm have been demonstrated in rodents treated with certain neuroleptics. Use cautiously in persons who will be exposed to extreme heat.

Phenothiazines may diminish the effect of oral anticoagulants. Phenothiazines can produce alpha-adrenergic blockade. Concomitant use of phenothiazines with propranolol increases plasma levels of both drugs. Concurrent use of phenothiazines may counteract antihypertensive effects of guanethidine and related compounds. Thiazide diuretics may accentuate the orthostatic hypotension that may occur with phenothiazines. Phenothiazines may lower the convulsive threshold and may also precipitate phenytoin toxicity; dosage adjustments of anticonvulsants may be necessary. If neuromuscular reactions occur in pregnant women, or in children, permanently stop neuroleptic therapy. Patients should not receive 'Stelazine' 48 hours before or 24 hours after myelography with the contrast medium metrizamide. The presence of phenothiazines may produce false positive phenylketonuria (PKU) test results.

**Adverse Reactions:** Drowsiness, dizziness, skin reactions, rash, dry mouth, insomnia, amenorrhea, fatigue, muscular weakness, anorexia, lactation, blurred vision. Neuromuscular (extrapyramidal) reactions: motor restlessness, dystonias, pseudo-parkinsonism, tardive dyskinesia, and a variant, tardive dystonia.

**Other adverse reactions reported with Stelazine (trifluoperazine HCl, SK&F) or other phenothiazines:** Some adverse effects are more frequent or intense in specific disorders (e.g., mitral insufficiency or pheochromocytoma).

Grand mal and petit mal convulsions, particularly in the presence, or with history, of EEG abnormalities; altered cerebrospinal fluid proteins; cerebral edema; prolongation and intensification of the action of C.N.S. depressants, atropine, heat, and organophosphorus insecticides; nasal congestion, headache, nausea, constipation, obstipation, adynamic ileus, ejaculatory disorders/impotence, priapism, atonic colon, urinary retention, miosis and mydriasis; reactivation of psychotic processes, catatonic-like states, hypotension (sometimes fatal); cardiac arrest; leukopenia, eosinophilia, pancytopenia, agranulocytosis, thrombocytopenic purpura, hemolytic anemia, aplastic anemia, jaundice, biliary stasis, hyperglycemia, hypoglycemia, glycosuria, menstrual irregularities, galactorrhea, gynecomastia, false positive pregnancy tests, photosensitivity, itching, erythema, urticaria, eczema up to exfoliative dermatitis, asthma, laryngeal edema, angioneurotic edema, anaphylactoid reactions, peripheral edema; reversed epinephrine effect; hyperpyrexia; mild fever after large I.M. doses; increased appetite; increased weight; a systemic lupus erythematosus-like syndrome; pigmentary retinopathy; with prolonged administration of substantial doses, skin pigmentation, epithelial keratopathy, and lenticular and corneal deposits; neuroleptic malignant syndrome, which may be fatal; EKG changes—particularly nonspecific, usually reversible Q and T wave distortions—have been observed. Temporary nausea, vomiting, dizziness, and tremulousness may follow abrupt cessation of high-dose therapy. NOTE: Sudden death in patients taking phenothiazines [apparently due to cardiac arrest or asphyxia due to failure of cough reflex] has been reported.

## SK&F LAB CO.

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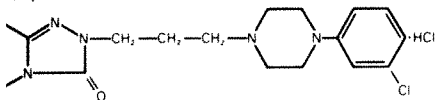
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# Desyrel® Dividose®

## (trazodone HCl)

### DESCRIPTION

Desyrel® (trazodone hydrochloride) is an antidepressant chemically unrelated to tricyclic, tetracyclic, or other known antidepressant agents. It is a triazoloindole derivative designated (4-[3-chlorophenyl]-1-piperazinyl)propyl-1,2,4-triazolo[4,3-a]pyridin-3(2H)-one hydrochloride. Desyrel is a white odorless crystalline powder which is freely soluble in water. Its molecular weight is 408.3. The empirical formula is  $C_{19}H_{22}ClN_5O$  and the structural formula is represented as follows:



Desyrel is supplied for oral administration in 50 mg, 100 mg, 150 mg, and 300 mg tablets.

1. Tablets, 50 mg, contain the following inactive ingredients: dibasic calcium phosphate, microcrystalline cellulose, ethylcellulose, FD&C Yellow No. 6 (aluminum lake), magnesium stearate, povidone, sodium starch glycolate, and starch (corn).

2. Tablets, 100 mg, contain the following inactive ingredients: dibasic calcium phosphate, microcrystalline cellulose, ethylcellulose, lactose, magnesium stearate, povidone, sodium starch glycolate, and starch (corn).

3. Tablets, 150 mg, contain the following inactive ingredients: microcrystalline cellulose, FD&C Yellow No. 6 (aluminum lake), magnesium stearate, pregelatinized starch, and croscarmellose.

4. Tablets, 300 mg, contain the following inactive ingredients: microcrystalline cellulose, FD&C Yellow No. 6 (aluminum lake), magnesium stearate, pregelatinized starch, and croscarmellose.

### PHARMACOLOGY

The mechanism of Desyrel's antidepressant action in man is not fully understood. In animals, it selectively inhibits serotonin uptake by brain synaptosomes and potentiates the release of serotonin induced by the serotonin precursor, 5-hydroxytryptophan. Cardiac conduction of Desyrel in the anesthetized dog are qualitatively dissimilar and quantitatively pronounced than those seen with tricyclic antidepressants. Desyrel is not a monoamine oxidase inhibitor and, unlike amphetamine-type drugs, does not stimulate the central nervous system.

Desyrel is well absorbed after oral administration without selective localization in any tissue. When Desyrel is taken shortly after ingestion of food, there may be an increase in the rate of absorption, a decrease in maximum concentration and a lengthening in the time to peak concentration. Peak plasma levels occur approximately one hour after dosing. Desyrel is taken on an empty stomach or two hours after dosing when taken with food. Desyrel is biphasic, consisting of an initial phase (half-life 3-6 hours) followed by a terminal phase (half-life 5-9 hours), and is unaffected by the presence or absence of food. The clearance of Desyrel from the body is sufficiently variable; in some patients it may accumulate in the plasma.

In patients who responded to Desyrel, one-third of the inpatients and one-half of the outpatients had a significant therapeutic response by the end of the first week of treatment. Surveys of all responders demonstrated a significant therapeutic effect by the end of the first week. One-fourth of responders required 2-4 weeks for a significant therapeutic response.

### INDICATIONS AND USAGE

Desyrel is indicated for the treatment of depression. The efficacy of Desyrel has been established in both inpatient and outpatient settings and for depressed patients with and without prominent anxiety. The depressive illness of patients studied corresponds to the Major Depressive Episode criteria of the American Psychiatric Association's Diagnostic and Statistical Manual, 4th Edition.

Depressive Episode implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning. It is associated with at least four of the following eight symptoms: change in appetite, change in sleep, motor agitation or retardation, loss of interest in usual activities or decrease in sexual interest, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and suicidal ideation or attempts.

### CONTRAINDICATIONS

Desyrel is contraindicated in patients hypersensitive to Desyrel.

### WARNINGS

Desyrel has been associated with the occurrence of priapism. In approximately 1/3 of the cases reported, surgical intervention was required and, in a few cases, permanent impairment of erectile function or impotence resulted. MALE PATIENTS WITH PROLONGED OR INAPPROPRIATE ERECTIONS SHOULD IMMEDIATELY DISCONTINUE THE DRUG AND CONSULT THEIR PHYSICIAN.

Patients should persist, promptly contact Bristol-Myers USPG Medical Services Department (1-800-429-5591 or 812/429-5000).

Desyrel has been associated with the occurrence of priapism. In approximately 1/3 of the cases reported, surgical intervention was required and, in a few cases, permanent impairment of erectile function or impotence resulted. MALE PATIENTS WITH PROLONGED OR INAPPROPRIATE ERECTIONS SHOULD IMMEDIATELY DISCONTINUE THE DRUG AND CONSULT THEIR PHYSICIAN.

Desyrel should be administered under the supervision of a urologist or a physician familiar with the procedure and should not be initiated without urologic consultation if the priapism has persisted for more than 24 hours.

Desyrel (trazodone hydrochloride) is not recommended for use during the initial recovery of myocardial infarction.

Desyrel should be used when administering Desyrel to patients with cardiac disease, and patients should be closely monitored, since antidepressant drugs (including Desyrel) have been associated with the occurrence of cardiac arrhythmias. Recent clinical studies in patients with pre-existing cardiac disease indicate that Desyrel may be arrhythmogenic in patients in that population. Arrhythmias identified include isolated PVCs, ventricular tachycardia, and in two patients short episodes (3-4 beats) of ventricular tachycardia.

### PRECAUTIONS

The possibility of suicide in seriously depressed patients is inherent in the illness and may occur without significant remission occurs. Therefore, prescriptions should be written for the minimum number of tablets consistent with good patient management.

Desyrel, including orthostatic hypotension and syncope, has been reported to occur in patients receiving Desyrel. Concomitant administration of antihypertensive therapy with Desyrel may require a reduction in the dose of the antihypertensive drug.

Desyrel is known about the interaction between Desyrel and general anesthetics, therefore, Desyrel should be discontinued for as long as clinically feasible.

Desyrel, like all antidepressants, the use of Desyrel should be based on the consideration of the potential benefits of therapy outweigh potential risk factors.

### Information for Patients:

Desyrel has been reported to occur in patients receiving Desyrel, patients with prolonged or inappropriate penile erection should immediately discontinue the drug and consult their physician (see WARNINGS).

Desyrel may impair the mental and/or physical ability required for the performance of potentially hazardous tasks, such as operating an automobile or machinery; the patient should be cautioned accordingly.

Desyrel may enhance the response to alcohol, barbiturates, and other CNS depressants.

Desyrel should be given shortly after a meal or light snack. Within any individual patient, total absorption may be up to 20% higher when the drug is taken with food rather than on an empty stomach.

### Laboratory Tests:

Occasional low white blood cell and neutrophil counts have been noted in patients receiving Desyrel® (trazodone hydrochloride). These were not considered clinically significant and did not necessitate discontinuation of the drug; however, the drug should be discontinued in any patient whose white blood cell count or absolute neutrophil count falls below normal levels. White blood cell and differential counts are recommended for patients who develop fever and sore throat (or other signs of infection) during therapy.

### Drug Interactions:

Increased serum digoxin or phenytoin levels have been reported to occur in patients receiving Desyrel concurrently with either of those two drugs.

It is not known whether interactions will occur between monoamine oxidase (MAO) inhibitors and Desyrel. Due to the absence of clinical experience, if MAO inhibitors are discontinued shortly before or after to be given concomitantly with Desyrel, therapy should be initiated cautiously with gradual increase in dosage until optimum response is achieved.

### Therapeutic Interactions:

Concurrent administration with electroshock therapy should be avoided because of the absence of experience in this area.

There have been reports of increased and decreased prothrombin time occurring in Coumadin-treated patients who take Desyrel.

### Carcinogenesis, Mutagenesis, Impairment of Fertility:

No drug- or dose-related occurrence of carcinogenesis was evident in rats receiving Desyrel in daily oral doses up to 300 mg/kg for 18 months.

### Pregnancy Category C:

Desyrel has been shown to cause increased fetal resorption and other adverse effects on the fetus in two studies using the rat when given at dose levels approximately 30-50 times the proposed maximum human dose. There was also an increase in congenital anomalies in one of three rabbit studies at approximately 15-50 times the maximum human dose. There are no adequate and well-controlled studies in pregnant women. Desyrel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

### Nursing Mothers:

Desyrel and/or its metabolites have been found in the milk of lactating rats, suggesting that the drug may be secreted in human milk. Caution should be exercised when Desyrel is administered to a nursing woman.

### Pediatric Use:

Safety and effectiveness in children below the age of 18 have not been established.

### ADVERSE REACTIONS

Because the frequency of adverse drug effects is affected by diverse factors (e.g., drug dose, method of detection, physician judgment, disease under treatment, etc.) a single meaningful estimate of adverse event incidence is difficult to obtain. This problem is illustrated by the variation in adverse event incidence observed and reported from the inpatients and outpatients treated with Desyrel. It is impossible to determine precisely what accounts for the differences observed.

### Clinical Trial Reports:

The table below is presented solely to indicate the relative frequency of adverse events reported in representative controlled clinical studies conducted to evaluate the safety and efficacy of Desyrel.

The figures cited cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors often differ from those which prevailed in the clinical trials. These incidence figures, also, cannot be compared with those obtained from other clinical studies involving related drug products and placebo as each group of drug trials is conducted under a different set of conditions.

	Treatment-Emergent Symptom Incidence			
	Inpts		Outpts	
	D	P	D	P
Number of Patients	142	95	157	158
% of Patients				
Reporting				
Allergic				
Skin Condition/Edema	2.8	1.1	7.0	1.3
Autonomic				
Blurred Vision	6.3	4.2	14.7	3.8
Constipation	7.0	4.2	7.6	5.7
Dry Mouth	14.8	8.4	33.8	20.3
Cardiovascular				
Hypertension	2.1	1.1	1.3	-
Hypotension	0.0	1.1	3.8	0.0
Shortness of Breath	2.8	1.1	1.3	0.0
Syncope	2.8	2.1	4.5	1.3
Tachycardia/Palpitations	0.0	0.0	7.0	7.0
CNS				
Anger/Hostility	3.5	6.3	1.3	2.5
Confusion	4.9	0.0	5.7	7.6
Decreased Concentration	2.8	2.1	1.3	0.0
Drowsiness	2.1	0.0	-	0.0
Disorientation	19.7	5.3	28.0	15.2
Dizziness/Lightheadedness	23.9	6.3	40.8	19.5
Excitement	1.4	1.1	5.1	5.7
Fatigue	11.3	4.2	5.7	2.5
Headache	9.9	5.3	19.8	15.8
Insomnia	9.9	10.5	6.4	12.0
Impaired Memory	1.4	0.0	-	-
Nervousness	14.8	10.5	6.4	8.2
Gastrointestinal				
Abdominal/Gastric Disorder	3.5	4.2	5.7	4.4
Bad Taste in Mouth	1.4	0.0	0.0	0.0
Diarrhea	0.0	1.1	4.5	1.9
Nausea/Vomiting	9.9	1.1	12.7	9.5
Musculoskeletal				
Musculoskeletal Aches/Pains	5.6	3.2	5.1	2.5
Neurological				
Incoordination	4.9	0.0	1.9	0.0
Paresthesia	1.4	0.0	0.0	-
Tremors	2.8	1.1	5.1	3.8
Sexual Function				
Decreased Libido	-	1.1	1.3	-
Other				
Decreased Appetite	3.5	5.3	0.0	-
Eyes Red/Tired/Itching	2.8	0.0	0.0	0.0
Head Full/Heavy	2.8	0.0	0.0	0.0
Malaise	2.8	0.0	0.0	0.0
Nasal/Sinus Congestion	2.8	0.0	5.7	3.2
Nightmares/Vivid Dreams	-	1.1	5.1	5.7
Sweating/Clamminess	1.4	1.1	-	-
Tinnitus	1.4	0.0	0.0	-
Weight Gain	1.4	0.0	4.5	1.9
Weight Loss	-	3.2	5.7	2.5

\* Incidence less than 1%.

D = Desyrel P = Placebo

Occasional sinus bradycardia has occurred in long-term studies.

above, the following adverse events have been reported to occur in association with the use of Desyrel® (trazodone hydrochloride) in the controlled clinical studies: akathisia, allergic reaction, anemia, chest pain, delayed urine flow, early menses, flatulence, hallucinations/delusio hematuria, hypersalivation, hypomania, impaired speech, impotence, increased appetite, increased libido, increased urinary frequency, missed periods, muscle twitches, numbness, retrograde ejaculation.

### Postintroduction Reports:

Although the following adverse reactions have been reported in Desyrel users, the causal association has neither been confirmed nor refuted.

Voluntary reports received since market introduction include the following: agitation, alopecia, anorexia, ataxia, breast enlargement or engorgement, diplopia, edema, extrapyramidal symptoms, grand mal seizures, hallucinations, hemolytic anemia, hyperbilirubinemia, leukopenia, jaundice, lactation, liver enzyme alterations, methemoglobinemia, nausea/vomiting (most frequent), paresthesia, priapism (See WARNINGS and PRECAUTIONS, Information for Patients), some patients have required surgical intervention), pruritis, psychosis, rash, stupor, urinary retention, urticaria, vasodilation, vertigo and weakness.

Cardiovascular system effects which have been reported include the following: conduction block, orthostatic hypotension and syncope, palpitations, bradycardia, atrial fibrillation, myocardial infarction, cardiac arrest, arrhythmia, and ventricular ectopic activity, including ventricular tachycardia (see WARNINGS).

### OVERDOSE

#### Animal Oral LD<sub>50</sub>

The oral LD<sub>50</sub> of the drug is 610 mg/kg in mice, 486 mg/kg in rats, and 560 mg/kg in rabbits.

#### Signs and Symptoms:

Death from overdose has occurred in patients ingesting Desyrel (trazodone hydrochloride) and other drugs concurrently (namely, alcohol, alcohol + chloral hydrate + diazepam, a barbiturate, chlorazepate, or propofol).

The most severe reactions reported to have occurred with overdose of Desyrel alone have been priapism, respiratory arrest, seizures, and EKG changes. The reactions reported infrequently have been drowsiness and vomiting. Overdose may cause an increase in incidence or severity of any of the reported adverse reactions (see ADVERSE REACTIONS).

#### Treatment:

There is no specific antidote for Desyrel. Treatment should be symptomatic and supportive the case of hypotension or excessive sedation. Any patient suspected of having taken overdose should have the stomach emptied by gastric lavage. Forced diuresis may be useful facilitating elimination of the drug.

### DOSEAGE AND ADMINISTRATION

The dosage should be initiated at a low level and increased gradually, noting the clinical response and any evidence of intolerance. Occurrence of drowsiness may require the administration of a major portion of the daily dose at bedtime or a reduction of dosage. Desyrel should be taken shortly after a meal or light snack. Symptomatic relief may be seen during first week, with optimal antidepressant effects typically evident within two weeks. Twenty percent of those who respond to Desyrel require more than two weeks (up to four weeks) drug administration.

#### Usual Adult Dosage:

An initial dose of 150 mg/day in divided doses is suggested. The dose may be increased by 50 mg/day every three to four days. The maximum dose for outpatients usually should not exceed 400 mg/day in divided doses. Inpatients (i.e., more severely depressed patients) may be given up to but not in excess of 600 mg/day in divided doses.

#### Maintenance:

Dosage during prolonged maintenance therapy should be kept at the lowest effective level. Once an adequate response has been achieved, dosage may be gradually reduced, subsequent adjustment depending on therapeutic response.

Although there has been no systematic evaluation of the efficacy of Desyrel beyond two weeks, it is generally recommended that a course of antidepressant drug treatment should be continued for several months.

### HOW SUPPLIED

#### Desyrel (trazodone hydrochloride)

Tablets, 50 mg — round, orange/scored, film-sealed (imprinted with Desyrel and MJ 100)  
NDC 0087-0775-41 Bottles of 100  
NDC 0087-0775-43 Bottles of 1000  
NDC 0087-0775-42 Cartons of 100 Unit Doses

Tablets, 100 mg — round, white/scored, film-sealed (imprinted with Desyrel and MJ 100)  
NDC 0087-0776-41 Bottles of 100  
NDC 0087-0776-43 Bottles of 1000  
NDC 0087-0776-42 Cartons of 100 Unit Doses

Tablets, 150 mg — orange, in the Dividose® tablet design (imprinted with MJ and 778 on front, "50", "50", "50" on reverse)  
NDC 0087-0778-43 Bottles of 100  
NDC 0087-0778-44 Bottles of 500

Tablets, 300 mg — yellow, in the Dividose® tablet design (imprinted with MJ and 796 on front, "100", "100", "100" on reverse)  
NDC 0087-0796-41 Bottles of 100

U.S. Patent No. 4,215,104

Store at room temperature. Protect from temperatures above 104°F (40°C).

Dispense in tight, light-resistant container (USP).

### REFERENCES

- Williams JBW, Ed: Diagnostic and Statistical Manual of Mental Disorders-III, American Psychiatric Association May, 1980.
- Brindley GS: New treatment for priapism, *Lancet*, July 28, 1984, ii 220.
- Goldstein I, et al: Pharmacologic detumescence: The alternative to surgical shunting, *Urology* 1986;135 (4 Pt 2):308A.
- Brindley GS: Pilot experiments on the actions of drugs injected into the human cavernosus penis, *Br J Pharmacol*, 1986;87:495-500.
- Padma-Nathan H, et al: Treatment of prolonged or priapistic erections following intracavernosal papaverine therapy, *Semin Urol* 1986;4(4):236-238.
- Lee TF, et al: Priapism: A refined approach to diagnosis and treatment, *J Urol* 1986;136:104-110.
- Fabre LF, Feighner JP: Long-term therapy for depression with trazodone, *J Clin Psychol* 1983; 44(1):17-21.

**Mead Johnson**  
PHARMACEUTICALS

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# When Insomnia Complicates Depression

Consider

## Desyrel<sup>®</sup> Dividose<sup>®</sup> (trazodone HCl)

Helps relieve insomnia symptoms  
associated with depression  
and treats the depression



Unique 300 mg and 150 mg  
Dividose tablets make daily  
dosing flexible and easy.  
Maximum dosage is 400 mg/d  
in divided doses for outpatients  
and 600 mg/d in divided doses  
for inpatients. Initial therapy is  
150 mg/d of Desyrel Dividose in  
divided doses.

**Mead Johnson**  
PHARMACEUTICALS



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Please see prescribing information on following page.

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